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The American Journal of Medicine

VOL. V SEPTEMBER, 1948 No. 3

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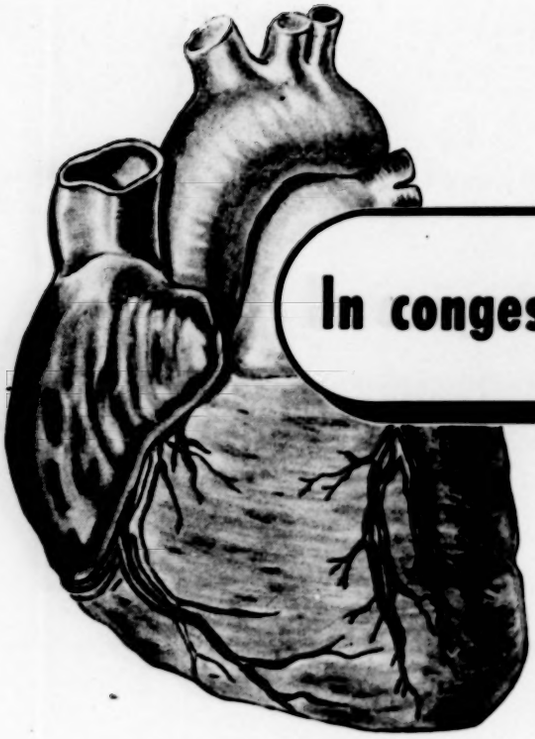

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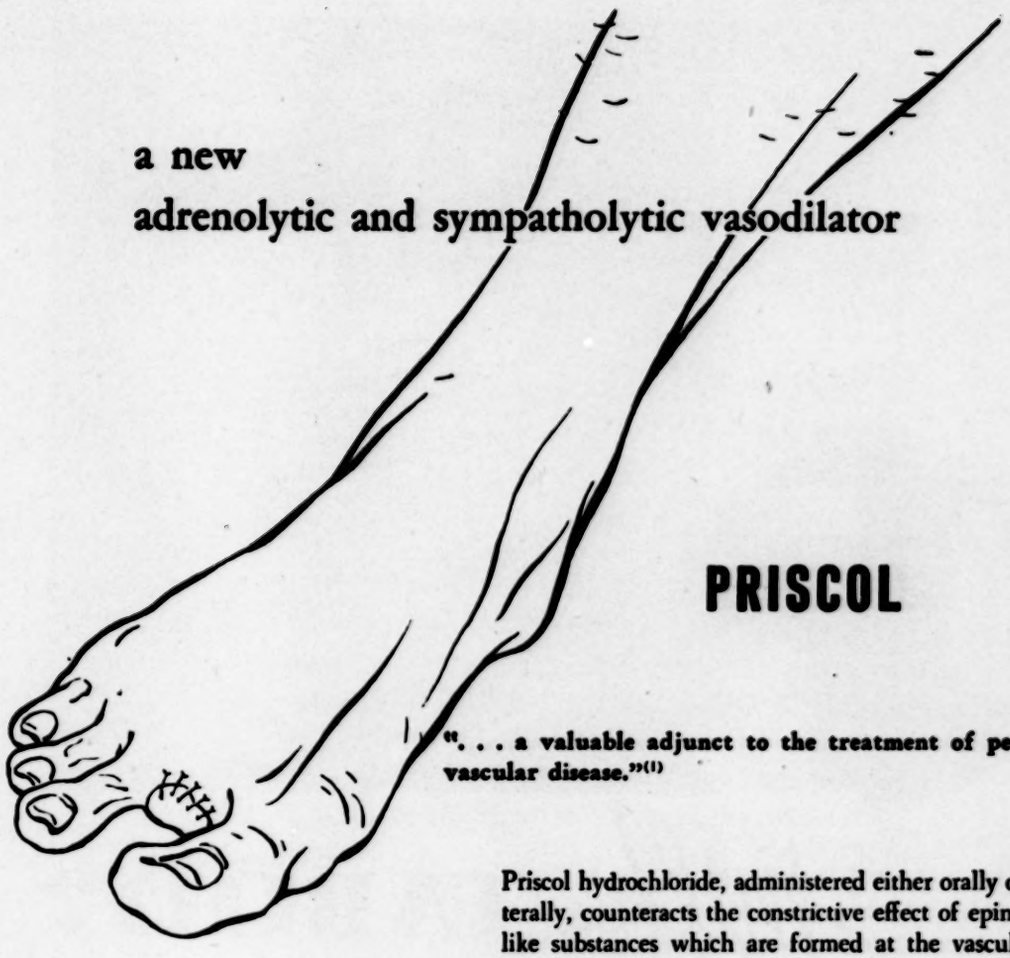

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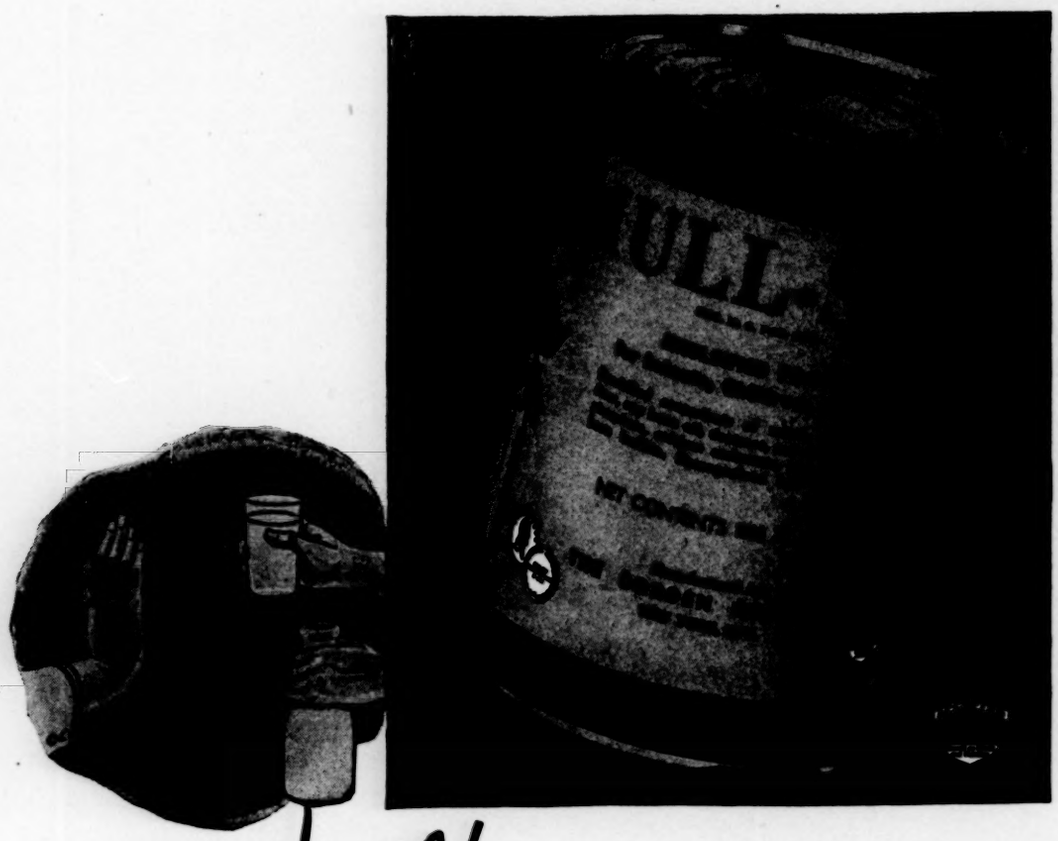

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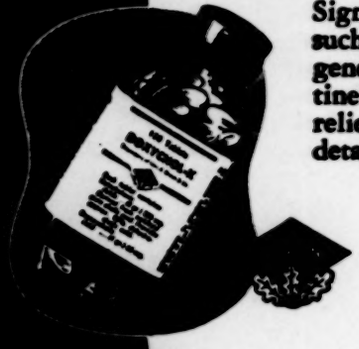

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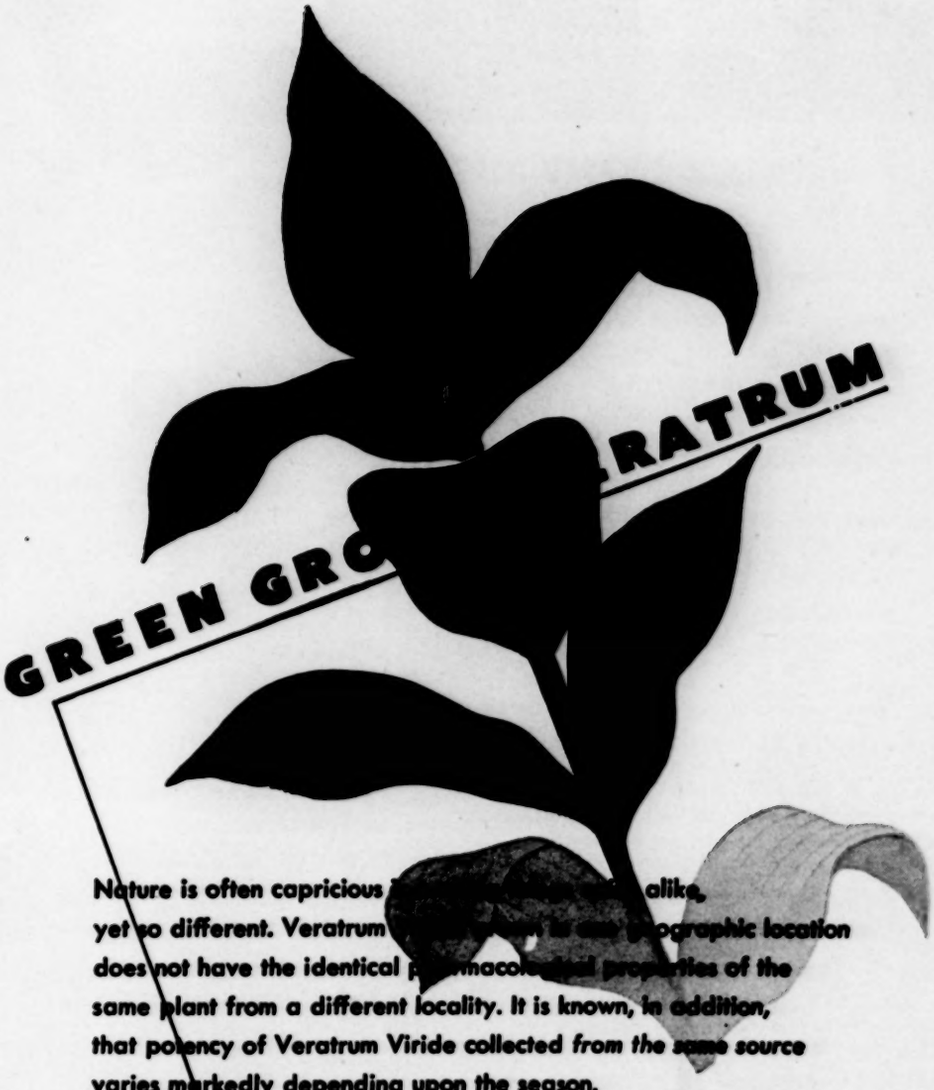

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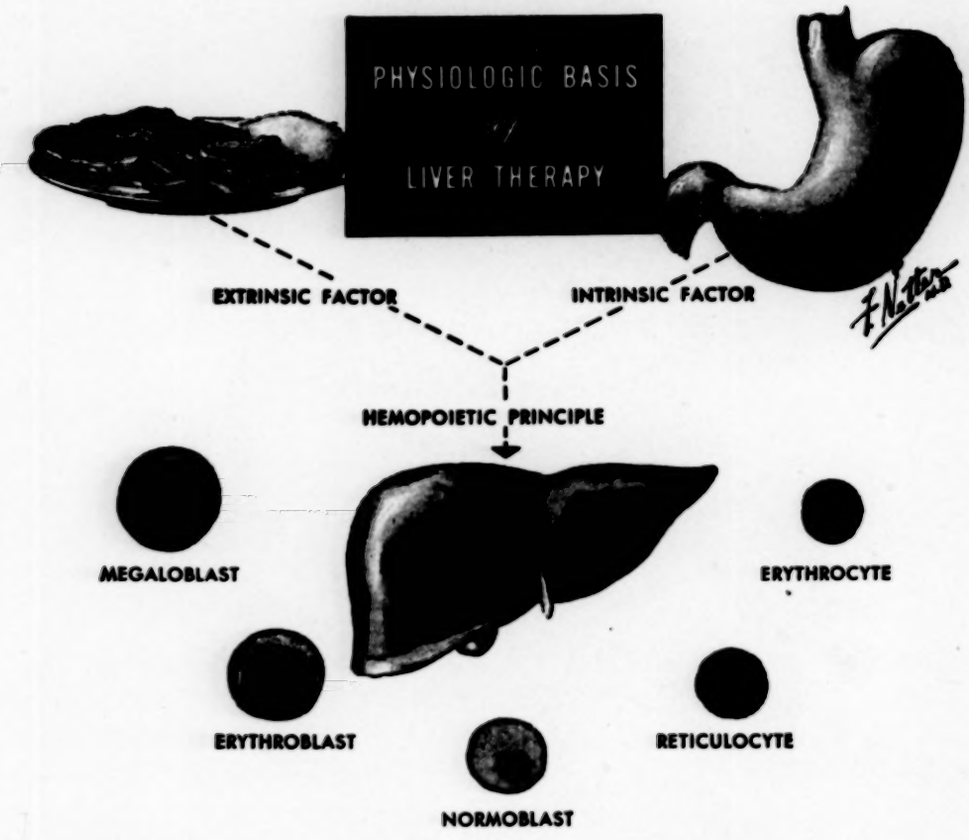

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1. Duca, C. J., and Scudi, J. V.: Proc. Soc. Exper. Biol. & Med. 66: 123 (1947).
2. Scudi, J. V., and Duca, C. J.: J. Urol. (to be published).

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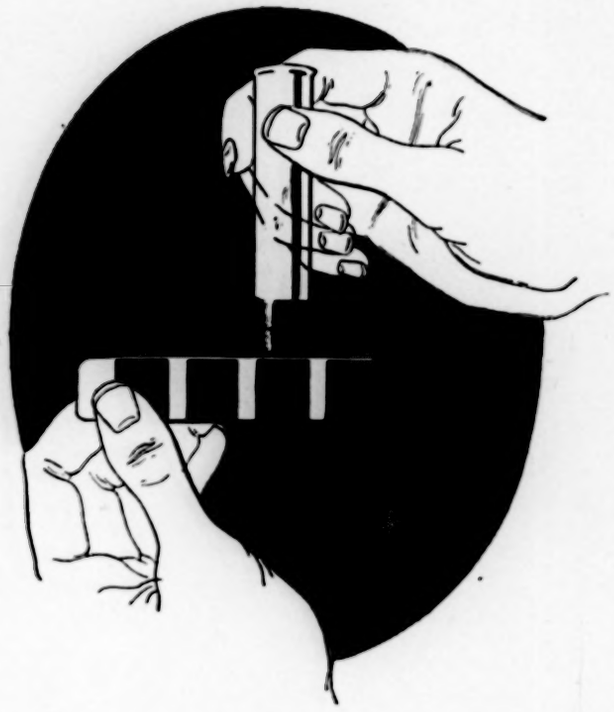

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The American Journal of Medicine

VOL. V SEPTEMBER, 1948 No. 3

Editorial

Coronary Arteries as End Arteries

THE question whether the coronary arteries are end arteries has been subjected to vigorous discussion for many decades. Intense interest in this problem has been provoked not only because of its scientific importance but also because of the direct clinical implications for our understanding of angina pectoris and acute myocardial infarction. The impossibility of measuring coronary flow in man during life and the manifold variations in the technics of postmortem studies in man and in experimental conditions in animals have led to conflicting and contradictory opinions. Differences between the architecture of the coronary tree in the dog and man have not always been appreciated.

The issue also has been confused by diverse interpretations of the term "end artery." To the anatomist an end artery is an artery which does not communicate with other arteries through any anastomotic connection so that its capillary bed receives blood from no other artery. To the physiologist an end artery is an artery which alone supplies sufficient blood to an area to maintain its function and integrity; when this vessel is occluded, the dependent area undergoes loss of function or necrosis because other arteries do not supply the given area sufficiently. These two definitions differ widely from each other; anatomic studies in other parts of the body have repeatedly demonstrated interarterial communication with vessels which physiologically are clearly end arteries.

Since Leonardo da Vinci, in one of his magnificent sketches, portrayed intercommunication between the coronary arteries, the interest and debate on this question have been almost continuous. Cohnheim and Schulthess-Rechberg in 1881[1] stated as a result of their studies that the coronary arteries were anatomic end arteries. It has, however, gradually become the consensus that connections exist normally between the coronary arteries, either directly or by way of fine communications of an arteriolar or capillary diameter.[2,3] These anastomoses are readily demonstrated by the simple observation that colored watery solutions which reach the capillary bed when injected into one coronary artery promptly appear in the other coronary arteries and their ramifications.[4]

The physiologic significance of these interarterial connections, their exact nature and the circumstances which may lead to their magnification have been the subject of intensive study during the past decades. Wiggers[5] has cogently remarked that "from a pathological standpoint it has long been accepted that the coronaries are terminal arteries, for when plugged by emboli or

[1] COHNHEIM, J. and SCHULTHESS-RECHBERG, A. Ueber die Folgen der Kranzarterienverschliessung für das Herz. *Virchows Arch. f. path. Anat.*, 85: 503, 1881.

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[5] WIGGERS, C. J. The physiology of the coronary circulation. In LEVY, R. L. Diseases of the Coronary Arteries and Cardiac Pain. New York, 1936. The Macmillan Co.

thrombi in man or when artificially occluded in animals an infarct results. The rapid necrosis of cardiac tissue could scarcely occur, were adequate anastomoses present." The failure of the supplied area to contract within one or two minutes following sudden occlusion and the electrocardiographic evidence of immediate injury are further manifestations of functional inadequacy as is indeed the common catastrophic clinical experience with patients suffering from acute coronary occlusion. Experimentally in the dog, the area peripheral to the coronary ligature becomes swollen, cyanotic and engorged and the veins appear full. Prinzmetal[6] has recently reported that the amount of blood in such stagnant areas may be equal to two-thirds or more of the normal.

Satisfactory evidence clearly demonstrates, however, that the intercoronary anastomotic channels in the normal heart, while not preventing infarction after sudden occlusion, have some functional significance. Smith[7] observed that following experimental occlusion of the left anterior descending artery the area of infarction was smaller than the entire territory of the distribution of this artery and its branches. Many observers have noted variation in the size of the infarct following experimental occlusion of the left anterior descending coronary artery in the dog. Indeed, in a small proportion, gross infarction does not appear at all because of the richer intercoronary connections in the dog than in man. Furthermore, following the acute occlusion of a coronary artery in the normal dog heart, cannulation of the cut artery peripheral to the tie reveals retrograde flow amounting to as much as 5.8 cc. per minute.[8] By gasometric analysis this blood was found to be arterial in nature and therefore must have been derived from precapillary interarterial connections. Utilizing an injection mass which penetrates to vessels approximately 15 to 40 micra in diameter in the fixed state, corresponding to 30 to 80 micra in diameter in the fresh state, Schlesinger[4] has demonstrated that intercoronary channels in the normal human heart are usually less than this caliber. This mass, because of its physical properties, may reach the capillary level irregularly but does not fill it or enter the coronary venous system. Only approximately 15 per cent of normal hearts reveal interarterial communications of this size and, when found, they are few in number. In contrast, 98 per cent of hearts with arteries occluded by arteriosclerotic lesions reveal collateral channels which are much more numerous, occasionally visible to the naked eye and of great functional significance. This has been demonstrated in many hearts in which, despite complete occlusions, the potentially infarcted myocardium has been free of fibrosis or other structural abnormality.[9] Verification of this phenomenon experimentally has also been accomplished.[8,10]

When narrowing of the coronary arteries even to occlusion proceeds gradually, first in one part of the coronary tree and then in another, complete occlusion of two or even of all three main coronary arteries may be compatible with continued life.[9] Most patients exhibiting this condition, particularly when the third unoccluded artery is greatly narrowed, experience angina pectoris or congestive failure. Injection of such hearts demonstrates an extraordinarily rich network of anastomoses. All semblance of end arteries is lost. Available evidence indicates that two or more weeks are required for these anastomoses to become

[6] Prinzmetal, M., Bergman, H. C., Kruger, H. E., Schwartz, L. L., Simkin, B. and Sobin, S. S. Studies on the coronary circulation. III. Collateral circulation of beating human and dog hearts with coronary occlusion. *Am. Heart J.*, 35: 689, 1948.

[7] Smith, Fred M. The ligation of coronary arteries with electrocardiographic study. *Arch. Int. Med.*, 22: 8, 1918.

[8] Eckstein, R. W., Gregg, D. E. and Pritchard, W. H. The magnitude and time of development of the collateral circulation in occluded femoral, carotid and coronary arteries. *Am. J. Physiol.*, 132: 351, 1941.

[9] Blumgart, H. L., Schlesinger, M. J. and Zoll, P. M. Angina pectoris, coronary failure and acute myocardial infarction. The role of coronary occlusions and collateral circulation. *J. A. M. A.*, 116: 91, 1941.

[10] Blumgart, H. L., Gilligan, D. R., Zoll, P. M., Freedberg, A. S. and Schlesinger, M. J. Studies of experimentally produced intercoronary collateral circulation. *Tr. A. Am. Physicians*, 57: 152, 1942.

evident and a longer period for the development of such functionally significant connections following narrowing of the coronary arteries;[8–10] vasomotor and metabolic factors as well as the differential pressure gradients between occluded and non-occluded segments of the coronary arterial tree play important rôles.

The slow development of these collateral channels emphasizes the importance of bed rest and reduced activity for many weeks after acute myocardial infarction, contrary to the current tendency to advise earlier ambulation. Ample evidence exists that reduced cardiac work favors healing of the infarct, reduces the extent of myocardial damage, lessens liability to rupture and provides time for the development of these anastomotic channels. Similar considerations would seem to apply to patients in whom angina pectoris suddenly appears or in whom the frequency or intensity of the attacks suddenly increases. If one can exclude temporary factors causing an increased demand for blood (fever, anemia) or physiologic reduction in coronary flow (shock, tachycardia), the sudden inadequacy of blood supply may be ascribed to structural organic narrowing or occlusion.

Such sudden imbalance of coronary circulation must always be viewed with gravity for any new reduction in coronary flow may result seriously in extensive myocardial necrosis if excessive demand is placed upon the heart before equilibrium is re-established by full development of anastomotic pathways. The slow development of a richer anastomotic circulation is also apparently responsible for the occasional clinical improvement of patients with angina pectoris, the collateral channels acting to offset the narrowing, even occlusion, which has occurred.

HERRMAN L. BLUMGART, M.D.

Clinical Studies

A Study of Specialized Heart Tissue at Various Stages of Development of the Human Fetal Heart*

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One of the outstanding controversies in cardiac physiology has been that of the myogenic versus the neurogenic theory of activity. Neurogenic activity was favored in the earlier years when there was no known muscular connection between auricles and ventricles of the mammalian heart. Because nerves were known to cross the A-V groove, the impulse to the ventricle was assumed to pass over these. The heart is supplied by cholinergic (parasympathetic) and adrenergic (sympathetic) fibers, and recently it has been established that cholinergic (vagal) fibers are distributed to the S-A node, to auricular muscle, to the A-V node, to the main bundle (in some species to the proximal portions of the right and left limbs), to the coronary vessels but *not to ventricular muscle.* (Nonidez.)[1] Adrenergic fibers do not stain readily and for this reason their terminations have not been followed in detail. It is believed that they are distributed to the S-A and A-V nodes, to auricular muscle, possibly to more peripheral parts of the conducting system (Truex and Copenhaver),[2] to the coronary vessels (to which they are dilator) and, in addition, *to the ventricular muscle.* Most of these sympathetic trunks reach the ventricle by crossing the A-V sulcus superficially while others accompany the A-V bundle.

His[3] published the description of the A-V bundle in 1893 after which time the myogenic theory came into prominence and was almost exclusively accepted for many years because of the following reasons: (1) The bundle of His composed of nonnervous tissue had been shown to exist; (2) interruption of this pathway caused heart block; (3) interruption of other pathways did not cause heart block; (4) in the embryo cardiac pulsations precede growth of nerves into the heart; (5) the heart continues to beat when severed from the nervous system.

The myogenic theory seemed firmly established until 1940 when it was reported that although a conducting system containing Purkinje cells was present in ungulates, such a system was doubtless only vestigial in the horse and was not even present in man or in dogs. With the loss of a "bundle of His," discussion concerning the neurogenic theory was renewed. (Glomset and Glomset.)[4]

The need for reconsideration of the two theories was emphasized by description of the Wolff-Parkinson-White[5] syndrome, a condition which is diagnosed when a

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short P-R interval is associated with a prolonged QRS in the electrocardiogram of individuals prone to attacks of paroxysmal tachycardia. Wood, Wolferth and Geckeler[6] and Öhnell[7] among others have reported that auriculoventricular connections apart from the bundle of His and composed of ordinary heart muscle fibers were present in the hearts of individuals who during life had presented this syndrome.

Davies and Francis,[8] reviewed certain pertinent phases of cardiac anatomy and physiology in poikilo- and homothermic vertebrates. Although there is still diversity of opinion, they conclude that in birds and mammals muscle specialized for the initiation and conduction of the impulse (nodal and Purkinje tissue) has evolved and its distribution is described. Birds have a more extensive Purkinje system (especially in the atria) than do mammals; this is related to the far more rapid heart rates in birds. Their distinctive conclusions are:

"Collateral evidence supporting the view that nodal and Purkinje fibers are neomorphic developments in the hearts of mammals and birds is provided by their ontogeny in the mammal, minor variations in their disposition, and the occasional presence of muscular A-V connections in addition to the single A-V bundle in mammals.

"Since there is no histological specialization of the muscle fibers in any part of the heart in poikilothermic vertebrates, factors other than purely morphological must account for the different intrinsic rhythmicities possessed by the individual chambers of such hearts. A differential distribution between atria and ventricles of certain chemical substances known to be concerned in muscular contraction is described and may have a bearing on the problem."

Another valuable paper is that of Walls[9] who studied serial sections of human embryos. The focal point of his research is stated thus:

"Accounts of the development of the conducting tissue of the human heart are few, accompanying illustrations are fewer still, and only one writer, Sanabria,[10] has described the development of the entire system. But even more than these considerations, what prompted the present study was the desire to establish, if possible, whether the nodes and bundle appear, grow and develop as do other organs of the body or whether they are simply remnants of the junctional tissues found at the S-A and A-V rings." In a description of a 10 mm. embryo he writes: "There can be no question that whereas the A-V node represents a part of the original A-V canal destined to become structurally specialized, *the bundle is a new formation which arises from that primitive nodal tissue by a process of active growth.*" (Author's italics.)

That the bundle is a new development is a view favored also by Tandler[11] Retzer[12,13] Shaner[14] and Davies.[15] Most current texts of embryology hold to Mall's[16] conclusion that the bundle is "an embryological remnant of the atrial canal of which the posterior musculature connecting the sinus and ventricle never breaks down, although showing early in development changes in structure which differentiate it from the rest of heart muscle." Truex and Copenhaver[2] observed numerous, delicate, pale-staining nerve fibers passing from the larger nerve bundles in close contact with Purkinje fibers but were unable to identify any perifibrillar plexuses as described by Wilson,[17] Scaglia,[18] Blair and Davies[19] and Vitali.[20] They saw no "specialized terminations" on the Purkinje cells. However, they write "we could follow fine varicose fibers from their perivascular plexus to small club-shaped terminals on the surface of cardiac muscle fibers." The average diameter of heart muscle cells was found to be somewhat less than that of the Purkinje cell.

Our observations were undertaken to procure further evidence that in the human fetal heart specialized tissue either did or did not exist, was or was not accompanied by nerves, did or did not at early stages have the same appearance as ordinary heart muscle from which it later differenti-

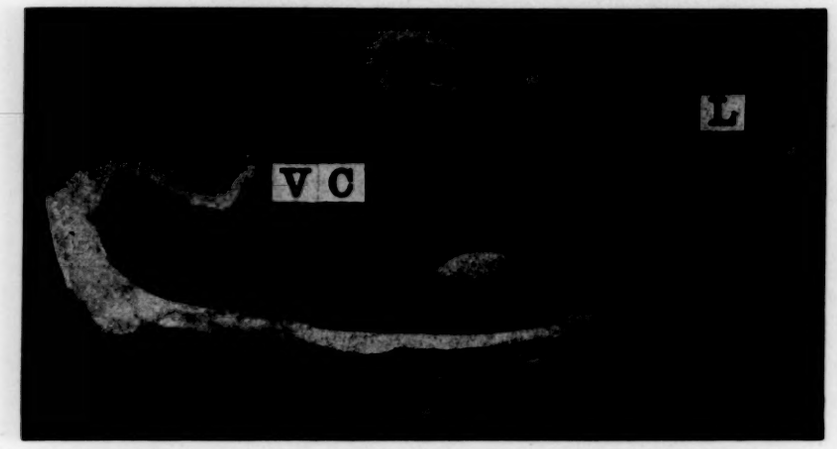


FIG. 1. Fetal heart of twenty weeks' gestation; photograph of reconstruction of S-A node. Enclosed area is orifice of superior vena cava. Projecting arm (L) indicates contact with muscles of left atrium. Arrows outline the commonly recognized "comma shaped structure, head anterior, lying in the sulcus terminalis." The smoothed surfaces are artifacts; at all surfaces numerous junctions between auricular and nodal tissue occur.

ates and finally that auriculoventricular connections apart from the bundle do or do not exist and persist.

MATERIAL AND METHODS

Four human fetal hearts were used in this investigation. They were from fetuses of fifteen and one-half, twenty, twenty-one and thirty-two weeks' gestation; the fetuses were approximately 12 cm., 16 cm., 17.5 cm. and 32 cm. c.r. length, respectively. Two of the hearts were fixed while still beating and the two others were preserved within two hours postmortem. They were injected with a fixative through all the great vessels and all the cavities to insure a rapid and adequate fixation of subendocardial structures. Each heart was then carefully dissected out and placed for varying lengths of time in the fixing solutions. Three preservatives were used: Zenker-formol, Bouin or chloral hydrate. After paraffin-rubber infiltration three hearts were cut into serial sections in the frontal plane and one in the sagittal plane. The following staining technics were used: Mallory's or Masson's trichrome for connective tissue and for general cytologic detail, Nonidez's bulk silver method for nerve staining. When the trichrome methods failed, Nonidez's technic supplied a fuller picture.

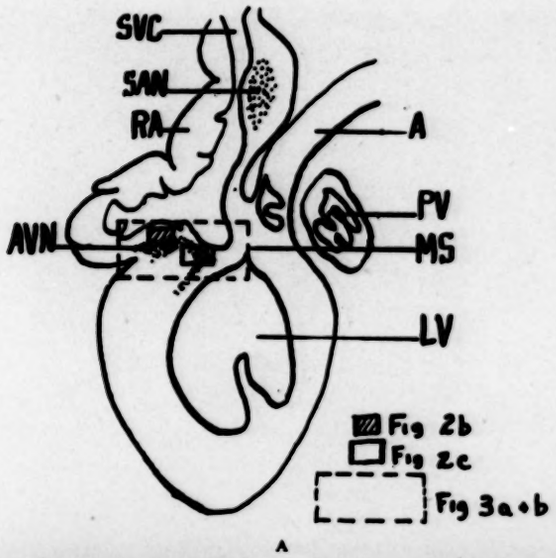
The youngest heart was sectioned at the Department of Embryology, Carnegie Institution of Washington. We are indebted to Dr. George W. Corner for the use of this specimen. The other hearts were obtained through the courtesy of the Department of Obstetrics at the Syracuse University College of Medicine and were sectioned by one of us (C. T. K.).

OBSERVATIONS

Fifteen and One-half Week Heart. The S-A node, A-V node, main bundle and bundle branches were observed in this heart. Cells of the S-A node were found to be more widely distributed than many authors have pictured them. This node extended medially and posteriorly around the superior caval orifice in addition to the better known portion which lies in the sulcus terminalis.

With the Mallory stain, the specialized cells of the nodes, bundle and branches were larger than atrial (Fig. 2 B) or ventricular cells (Fig. 2 C); their cytoplasm took less stain and was less granular. Cross striations were not seen in specialized cells although they were readily observed in cells of the myocardium. No striking cytologic differences could be observed between cells of the various parts of the conducting system.

The A-V node was located in the lower posterior part of the interatrial septum as found by all workers. Posterior (Fig. 3 A) and anterior (Fig. 3 B) atrial connections to it were found. These pathways were vividly shown in the slides in which the



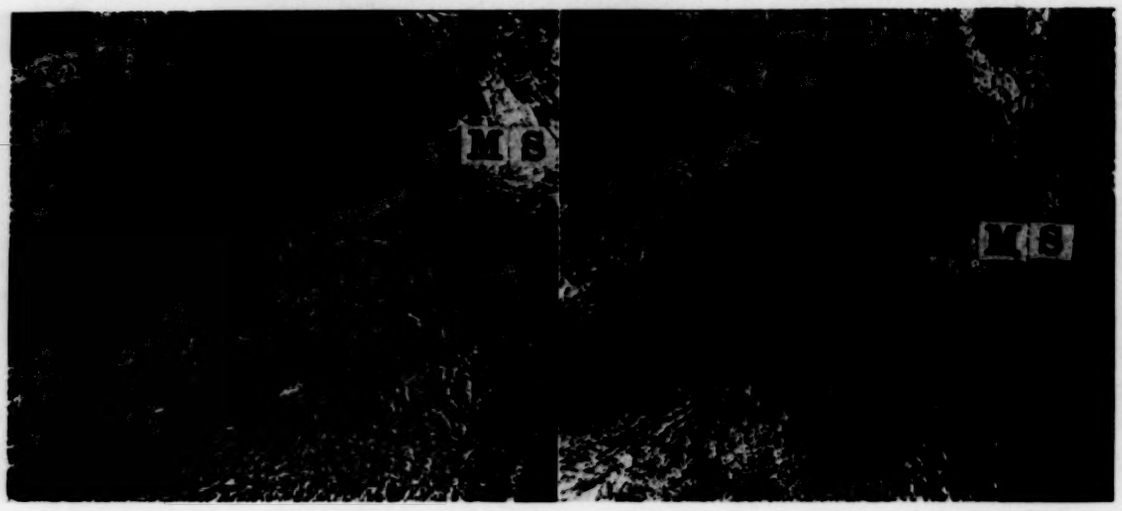
A

B C

FIG. 2. Fetal heart of fifteen and one-half weeks. A, pen sketch showing orientation. Mallory stain; B, portion of sagittal section through base of interatrial septum. Above lie parallel strands of dark staining auricular muscle (AM) and below the larger, paler specialized cells of the A-V node (N). × 500. C, above the large, pale nodal cells (N); strands of dark stained connective tissue produce lobulations; at lower edge is ventricular muscle (VM).

connective tissue was bright blue and the muscle cells deep red. The significance of these connections is discussed later. A sleeve of connective tissue surrounded the node but did not isolate it completely from atrial muscle. Extending from the A-V node were compact strands of cells which formed the main bundle. Right and left branches were recognized. Furthermore, on the right side of the ventricular septum more than one branch appeared. From the main bundle and from each of the branches numerous connections to septal muscle were seen. The main bundle and branches had a much thinner connective tissue sheath than the node. No appreciable space between special cells and the connective tissue sheath could be seen.

Sagittal sections were particularly favorable for demonstrating connections of any nature between atria and ventricles. Study and reconstructions of this heart established



A B

FIG. 3. Fetal heart of fifteen and one-half weeks; sagittal section. Figure 2A provides orientation. A-V node and proximal part of left branch indicated by black arrow heads; Mallory stain; × 55. A, tongue-like portion of membranous septum (MS) blocks anterior pathway (between white arrows) from S-A to A-V nodes. B, here the membranous septum (MS) is narrower and an anterior pathway continuous from the A-V node via the anterior atrial wall to the S-A node is present.

that although these cells, quite different from myocardial cells, formed the A-V node and bundle of His, nevertheless they were part of a continuous muscular connection between the atrium and the ventricles. This continuity has been observed in younger hearts by other workers (Mall,[16] Sanabria,[10] Walls)[9].

In addition to septal atrioventricular connections other bridges between atrial and ventricular muscle were observed which were composed entirely of ordinary cardiac muscle cells. (Fig. 4.) The significance of the muscular A-V connections which occur intermittently around the A-V orifices, but especially around the tricuspid opening, will be discussed later.

Our observations on the changes in microscopic appearance of bundle branch cells as they approach myocardial cells do not enlarge upon the descriptions given by previous investigators. Bundle cells lost their more rounded contour as they merged with the more elongated ventricular cells.

In sagittal sections a large artery was cut longitudinally as it ran through the A-V nodal tissue. This corresponds to branch number nine of Spalteholz.[21] The capillary spaces in node and bundle were less conspicuous than in the myocardium.

Twenty and Twenty-one Week Hearts. The S-A node in these hearts was identified more easily than in the younger specimen. It was found to occupy the same position described for the fifteen and one-half week heart, i.e., it formed the comma-shaped structure usually described and in addition extended medially and posteriorly around the superior caval orifice. The complete node was reconstructed in plastic, in wax and finally was cast in plaster. (Fig. 1.)

S-A nodal cells, rounder and less deeply stained than atrial muscle cells, were seen more clearly with the Masson stain. The atrial cells possessed more fibrillae and in places their cell boundaries were confluent. As was the case in the younger heart, anterior and posterior pathways, uninterrupted by connective tissue, were observed between S-A and A-V nodes which consisted of muscle and of specialized cells. However, we have not been able to reconstruct a connection consisting exclusively of specialized cells.

At this age the A-V node was a more compact structure. It had the same atrial connections as the younger heart, the more anterior of which reached the right side of the interatrial septum while the posterior connection extended to the left side of the

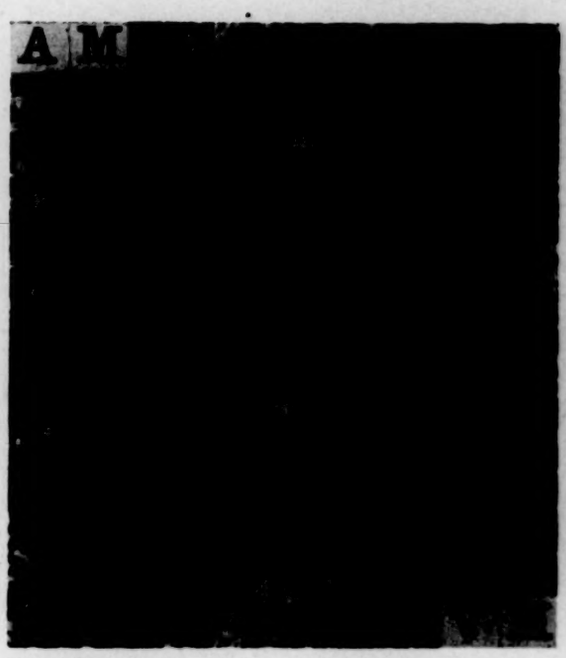


Fig. 4. Fetal heart of fifteen and one-half weeks; sagittal section; posterior-medial portion of tricuspid ring. A strand of atrial muscle (AM) from above passes through a funnel-shaped interruption in the darkly stained connective tissue A-V barrier to the ventricular muscle (VM); Mallory stain; × 350.

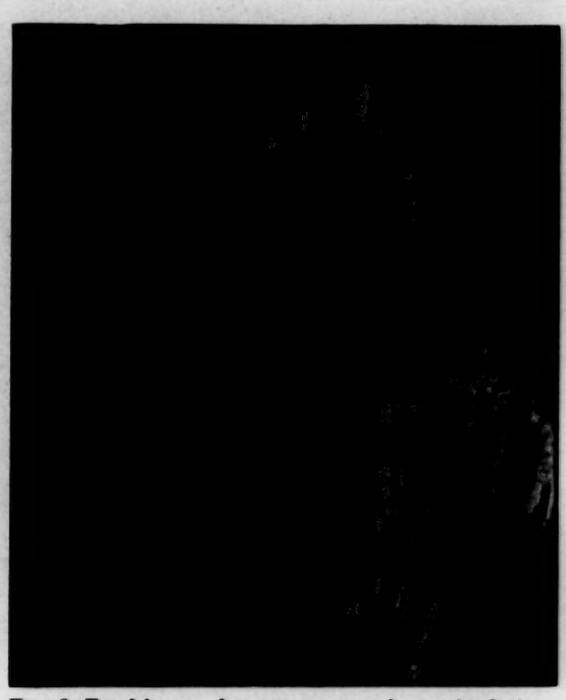


Fig. 5. Fetal heart of twenty-one weeks; sagittal view. Photograph of a reconstruction of the specialized cells which shows the more anterior right bundle branch (A), the extensive left branch (B), the main bundle (C), the A-V nodal region (D), with connections to the respective atrial walls through anterior (E) and posterior (F) pathways.

septum. The cells of a part of the node were arranged in a basket-work fashion (as described by Tawara)[22] which made connections to ordinary atrial muscle. In both hearts a thin slip of cells extended upward along the more anterior part of the right border of the membranous septum and became confluent with muscle of the atrial septum. Thus, four different pathways of atrial connection to the A-V node were observed: anterior to foramen ovale, from the posterior atrial wall along the base of the auricular septum and right and left connections in the septum from the more anterior part of the A-V node to the atrial musculature. (Fig. 5.)

From the A-V node cells comprising the main bundle extended downward through the membranous septum to lie on top of the ventricular septum. (Fig. 5.) In frontal section the right bundle branch (Fig. 6) was more anterior than the left and as the main bundle was followed through the septum more than one branch to the right ventricle could be seen. The left limb (Fig. 7) was the more extensive of the two. It extended broadly beneath the endocardium down the septal wall of the left ventricle. (Compare with Fig. 5.) Eventually it split into strands of cells going to the anterior papillary muscle, to the inferior papillary muscle and to the apical portions of the interventricular septum.

The main bundle gives branches directly to the septum at the more basal portion (Mahaim)[23] and indeed there are connections throughout the septum from the bundle branches.

The A-V node, bundle and branches were composed of cells recognizably different from ventricular cells. (Figs. 7 and 8.) The specialized cells contained larger amounts of clear cytoplasm, giving them a bloated appearance. Myofibrillae, although scarce and peripherally located, could be seen only in the limb cells. The only type of termination of strands of specialized cells which was seen (or for that matter has ever been described in the literature) was a gradual end-to-end transi-

6 7

FIG. 6. Fetal heart of twenty-one weeks; frontal section through the base of the interventricular septum showing the broad stump of the right bundle branch (RB), the beginning of the left branch (LB), the ventricular septum (VS), the septum membranaceum (MS), the base of the medial tricuspid leaflet (T) and the base of the mitral valve (M) attachment to the septum. Masson stain; × 105.

FIG. 7. Fetal heart of twenty weeks; frontal section at the base of the interventricular septum (VS) showing the membranous septum (MS), the main bundle (B) and the left branch (LB); silver stain; × 105.

tion into ordinary muscle. (Fig. 8.) We found nothing which could be called a myoneural junction between conducting and ordinary cells. Further study of the

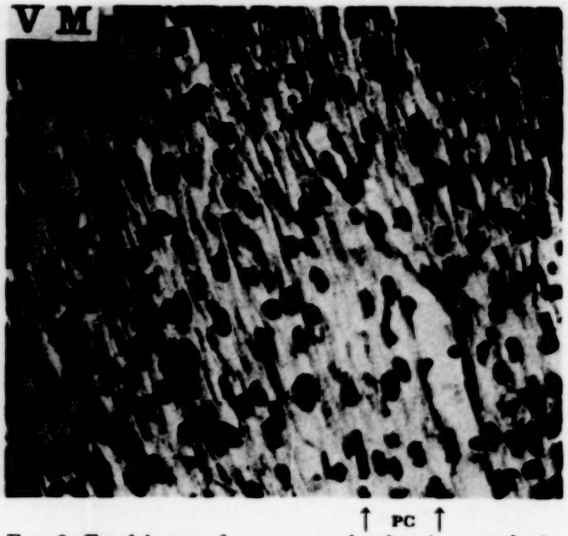


FIG. 8. Fetal heart of twenty weeks showing cytologic detail from base of a ventricular papillary muscle. At either side note parallel strands of cardiac muscle (VM); narrower diameter, deeper stained, marked cross striation. In lower center note a group of broader fibers, stained less deeply, having a few peripheral striations and a clear perinuclear space (PC). Note the transition from this band to the typical ventricular type at the top center; silver stain; × 500.

areas supplied by single Purkinje strands is in progress.

The main bundle was inclosed in heavy connective tissue in these hearts. Although there was space between nodal and connective tissue, it was thought that this was the result of technic of imbedding rather than actual. Study of these two and the older hearts added nothing new to our knowledge of the blood supply of the special tissues.

This was the only heart studied for nerves to the specialized tissue and myocardium. From preliminary studies it was evident that there were a number of darkly stained fibers (presumably parasympathetic postganglionic fibers or afferent fibers) to atrial structures and to the main bundle. Since sympathetic postganglionic fibers are not differentiated with the bulk silver method, it was impossible to study their distribution. The darkly stained fibers could not be followed for any appreciable distance along the branches of the main bundle of His.

Thirty-two Week Heart. Information on the S-A node is lacking in this heart since

FIG. 9. Fetal heart of thirty-two weeks; portion of a frontal section through the base of the interventricular septum to show the A-V node (N) imbedded in the dense connective tissue of the membranous septum (MS); Masson stain; × 125.

FIG. 10. Fetal heart of thirty-two weeks; frontal section through the upper part of the interventricular septum. The main bundle (B), right branch (RB), left branch (LB) and a septal branch (SB) are shown; Masson stain; × 125.

the block of tissue sectioned included only those structures below the level of the foramen ovale. The A-V node and main bundle were completely imbedded in the heavy connective tissue of the upper part of the membranous septum. (Fig. 9.) Cells of the node, bundle and limbs were still, at this stage of development of the heart, larger than myocardial cells. Relatively few myofibrillae were seen in their cytoplasm.

The left limb of the bundle came off more anteriorly than the right in this heart, in contrast to the condition found in the younger ones. At this stage of development the cells of the two limbs were even more strikingly different from ordinary cells than at earlier stages; they were longer and

FIG. 11. Fetal heart of thirty-two weeks; portion of the left branch (LB) lying beneath the endocardium (E); to the left the heavily stained myocardium (VM). Bundle cells are more faintly striated and have a clear perinuclear space similar to a "typical Purkinje cell."

possessed more fibrillae which showed striations. There was still a clear area around the centrally located nucleus, suggestive of the Purkinje type cell. (Fig. 11.) Both limbs could be followed for greater distance in the ventricles than in the younger specimens. The right limb (Fig. 10) had assumed greater proportions at this stage. In fact, except for its length, it was nearly the size of the left limb. There were numerous septal connections from the main bundle (one of which is seen in figure 10) and from the limbs which, with the report by Mahaim,[23] establishes these connections in the human heart. They have previously been seen in the guinea pig heart (Robb and Kaylor).[24] As the bundle branches approached the ventricular apices more and more specialized cells changed gradually into the strictly myocardial type of cell.

This heart has not yet been examined to determine whether muscular A-V bridges are present.

SUMMARY OF FINDINGS

In three of these hearts an S-A node was found which extended around almost the entire entrance of the superior vena cava into the right auricle, that is to say, the comma-shaped structure known to lie within

the sulcus terminalis is a part but not the whole of the S-A node. (Fig. 1.) Pathways uninterrupted by connective tissue make connections from this node to the A-V node. (Fig. 2A.) One of these extends from the posterior portion of the S-A node in the sulcus terminalis, then along the posterior atrial wall, thence horizontally along the A-V junctional area to the A-V node. (Fig. 3A.) Another extends from the anterior portion of the S-A node, anterior to the foramen ovale to the upper somewhat posterior portion of the A-V node along the "raphe" of Papez[25] which is deep to the interatrial band. (Fig. 3B.) Still other strands from the S-A node connect through the right and left portions of the interatrial septum to the more distal portions of the A-V node and proximal portions of the bundle. None of these pathways is composed exclusively of specialized tissue. On the contrary, specialized cells appear near the nodes but then spread out to make end-to-end transitions into the ordinary atrial muscle. Not one of these pathways is near either the epicardial or endocardial surface throughout.

The silver preparations of one heart indicate that there is a considerable supply of dark stained nerve fibers to the S-A and also to the A-V node. Because there is no differential stain available for sympathetic fibers, we have no observations on their course or terminations.

From the A-V node compact bundles of specialized cells stream distally forming the bundle of His which divides into two main outflows at the top of the interventricular septum. The left outflow has been described as a broad, flat sheet which eventually separates into anterior, posterior and septal portions. This we confirm. However, we report that the right outflow does *not* consist of one single limb as commonly stated (Fig. 5) although it is usually in discrete bands and not "sheet-like" as on the left. Connections from the main bundle and from all parts of the right and left branches to septal muscle are to be seen in all of these hearts. (Fig. 10.)

In general, the cells throughout the specialized system are alike and are different from either auricular or ventricular cells. This difference consists in the diameter being somewhat greater than that of ordinary cardiac muscle cells, the cytoplasm is clearer, there are fewer cross striations and a few peripheral myofibrillae are sometimes apparent. These cells stain less deeply with Masson, Mallory or silver technics than do ordinary muscle cells. (Figs. 6, 7 and 11.) In addition, the nodes are imbedded in connective tissue which is well differentiated with the Masson and Mallory stains. (Fig. 9.) The bundle, its branches and the Purkinje transitions into ordinary heart muscle are all enclosed in a connective tissue sheath. It is uncertain whether the small space within the sheath is an actual space during life. Our present opinion is that it may be caused by the fixing process.

We have seen nothing which could be considered to be an end organ. Whenever a Purkinje strand is followed peripherally it eventually undergoes gradual transition into an ordinary heart muscle fiber. This transition is always arranged end-to-end. A Purkinje strand never makes a right angle connection to a heart muscle cell. (Fig. 8.) We have made no new observation regarding the Purkinje-myocardial junctions nor the blood supply to this specialized tissue. We have never found an accessory bundle of His, i.e., more than one strand of specialized tissue connecting the auricle with the ventricle although we have found multiple A-V bridges of ordinary muscle.

COMMENTS

We agree with Truex and Copenhaver[2] whose comment regarding the moot question as to whether or not there are "typical Purkinje" cells in the human heart we commend and wish to quote:

"The existence of Purkinje fibers in various ungulates is unanimously accepted but their presence in dog and human hearts has been recently denied . . . In determining whether or not such fibers exist in man one must first decide what each author means when using the term "typical

Purkinje fiber." Is a given fiber considered typical in that it resembles the Purkinje fibers of ungulates, notwithstanding that even here it is possible for one to detect specie differences? Should a fiber be called typical only if it be of large size, has a clear cytoplasmic center, has a few peripherally placed myofibrillae with less marked striation, has nuclei in groups, and possesses a connective tissue sheath? . . . When each of these attributes of a supposedly typical Purkinje fiber is found to be highly variable from fiber to fiber and from specimen to specimen, it is not surprising to find a lack of agreement in the literature. It is our opinion that the attempts to identify and specifically classify every fiber encountered by means of highly variable yet characteristic criteria, are neither justified nor necessary. In our series of human specimens we have found many Purkinje fibers which are typical in size, myofibrillar content and arrangement, etc., as shown in Figure 4. However, in the same sections we have also observed less characteristic Purkinje fibers as well as questionable fibers we could not distinguish from cardiac muscle fibers."

Blair and Davies[19] preferred to use the term "Purkinje-like" to describe cells in the human bundle. We have chosen to use the indefinite appellation of "specialized" cells meaning presumably the same cells which Blair calls Purkinje-like and Truex and Copenhaver call Purkinje. Finally, in employing the term "specialized tissue" rather than "conducting tissue" we are making the term purely descriptive instead of allowing an implication of function to be included. While it is generally considered probable that these peculiar cells are the very agents which conduct the stimulus to the ventricle, nevertheless absolute proof that the sympathetic nerves which accompany the bundle and its branches have nothing to do with conduction is yet to be produced. Any cutting, crushing, ligation or injection procedure must of necessity damage these characteristic cells *and nerve fibers, too*, because of their intimate admixture.

The cells throughout the specialized system are similar, i.e., S-A, A-V and bundle cells are more like each other than are any of these like ordinary muscle. In the oldest of these hearts the cells of the specialized tissue are more unlike myocardial cells than in the younger hearts. Indeed the specialized cells undergo a more extensive change than do the ordinary myocardial cells. On this basis we agree with Gegenbaur,[26] Minervini,[27] Nonidez[1] and with Walls[9] that the specialized tissue in the embryo has a specific appearance and undergoes a gradual differentiation which none of the myocardial cells ever experience. Although these observations are limited and certainly do not offer any absolute proof, yet they are in accord with the opinions of Shaner[14] and of Davies and Francis[8] that the specialized tissue is an entity and not merely a persistent portion of the original cardiac tube. That truly muscular bridges connect the adult human auricle to the ventricle is also presumptive evidence that these bridges and the bundle of His have a different anlage because, although both have persisted, the cells of only the one have differentiated. The detail of changes in specialized and ordinary cardiac muscle tissue with age will need much further study.

Our observations on the S-A node differ from many others in that we find it far more extensive, offering thus more numerous contacts with auricular muscle especially deep in the septum and toward the left side. The several pathways, unobstructed by connective tissue which exist between the S-A and A-V nodes, are deeply placed in the atrial walls, a fact which makes experimental investigation difficult. Electrodes placed on either the epicardial or endocardial surface of the atrium would therefore record surface change under the electrodes but would give information neither for nor against the existence of deeper more direct pathways from one node to the other.

We find that the A-V system of specialized cells differs from the classical descriptions of Tawara,[22] Monckeberg[28] and most modern anatomic texts which allot both septal and lateral wall supplies entirely to

recurrent branches from the apical portions of the limbs. Mahaim[23] notes direct septal connections at the base; we find them throughout the septum. Reference to Ashman and Hull[29] will show that this point is of some importance to the analysis of electrocardiograms. Present day interpretations are based on the assumption that no such septal connections exist.

The constancy of appearance of more than one right branch is a matter that should be more thoroughly investigated. Walls[9] has also reported this condition. A connection along the anterior right edge of the membranous septum to one of the right branches might serve as an auriculoventricular conduction pathway if the main bundle were not functioning. Also if such an arrangement exists in common laboratory animals, one would need to investigate its relation to A-V block. Davies and Francis[8] remarked in this connection: "The anomalous results obtained by Krönecker and Busch[30] (1899), Imchanitzky[31] ('06) and Paukul[32] ('08) in the rabbit were shown by Cohn and Trendelenburg[33] ('10) and Lloyd[34] ('30) to be due to the presence of early branches emerging from the bundle above the site of injury; these are not present in the dog or cat.") Since such high connections are present in human fetal hearts, re-investigation in dogs and cats would be worth while.

Either this right-sided pathway, partly muscular, partly specialized tissue, or the truly muscular bridges found could serve as accessory routes when the Wolff-Parkinson-White syndrome is present. They also might be functioning when transient, alternating right and left types of branch bundle block are present. In a previous publication (Robb and Turman)[35] it had been suggested that the anatomic pathway was not the only determinant of the pathway for conduction. Naturally the pathway for conduction cannot be divorced from anatomic structure but physiologic refractoriness of an existent anatomic pathway can prevent conduction. If the ordinary pathway is refractory, an appropriately timed stimulus may pass over one of these accessory pathways. Thus, it is the refractory state (itself dependent on many factors) in relation to the arrival of stimuli which determines conduction pathways not mere anatomic continuity.

Kent[36] found muscular connections between the auricle and the ventricle on the right side, an observation which has been the source of much controversy. Wood, Wolferth and Geckeler,[6] Öhnell[7] and others have found such muscular connections in the hearts of individuals who had presented the Wolff-Parkinson-White[5] syndrome. Not all the slides in our collection have been searched for such connections. In two hearts where such search has been completed, muscular bridges were found. We do not know yet and only exhaustive examination of hearts of many ages will prove whether such bridges always persist and never (or infrequently) function, or whether such muscular bridges exist only rarely and then do function. At present we only know that they are present in some embryos and that they have persisted in some hearts when during life the Wolff-Parkinson-White syndrome was known to have been present.

This paper would be incomplete if we failed to emphasize the significance of the Purkinje transitions into heart muscle. Because these terminations are "axial," i.e., end-to-end, it must follow that if this specialized tissue is the conducting system and if a wave of depolarization sweeps over this tissue onto ordinary heart muscle, the direction of such a wave *normally* must be the same as the muscle fiber direction. Hence depolarization would proceed radially from endocardium to epicardium *only where fiber direction is also radial*, e.g., where the superficial muscles penetrate at the apices and at the trabeculated area. Presumably at the ventricular bases where fiber direction varies with different layers, several depolarization waves traveling in different planes would be present.

Separate strands of Purkinje tissue are found to supply adjacent muscular areas. Such a distribution ensures rapid and pre-

sumably orderly activation of muscle always in a plane parallel to fiber direction. Since there are multiple Purkinje connections, sequential activation of muscle strands is insured although spread in muscle syncytium will be limited to the area supplied by one Purkinje strand (because adjacent areas will be almost simultaneously active and refractory). This conception agrees with data of many physiologists who have measured surface spread and found it very limited, (e.g., Harris).[37] We believe that only under abnormal conditions, when adjacent areas are not simultaneously refractory, does muscular syncytial spread occur. That QRS (unlike P-R) is not directly proportional to heart mass and that abnormal beats have a longer QRS than normally conducted beats also would be in accord with this theory.

The lack of a stain which will differentiate sympathetic nerves prevents observations being made which would settle the point emphasized by Truex and Copenhaver:[3] "any consideration of the physiological mechanism of the conduction system, which is beyond the scope of the present investigation, must take into account the fact that large bundles of nerve fibers accompany the A-V bundle and its branches." Pale-staining nerves, presumably sympathetic, accompany the bundle and its branches and other adrenergic nerves cross the A-V groove. According to Nonidez,[1] these are distributed to ventricular muscle. Complete knowledge of the exact pathways, manner of termination and function of these nerves does not exist. The present day tendency is to overlook this gap in information and concede that the specialized tissue is "the conducting pathway." Because of juxtaposition, both kinds of tissue are destroyed by experimental procedures. We must realize that the exclusive allocation of the function of conduction to the specialized cells depends on *one* type of experiment. The method was to cut or crush the bundle and allow the animals to recover. The assumption was made that if the conducting tissue were nerve, regeneration would occur; if it were specialized cells, regeneration would not occur and the block would be permanent. The comment may be made that scar tissue barriers may prevent peripheral regeneration of axones. Such barriers are present following cutting, crushing, ligation or injection experiments at the base of the heart. Thus, we may say the presumptive (but not the absolutely proven) opinion is that the specialized tissue is the ordinary conducting pathway from auricle to ventricle. At times this pathway probably yields to one consisting of ordinary muscle fibers.

CONCLUSIONS

1. In four human fetal hearts studied, cells having characteristics similar to Purkinje cells were found.

2. One group of specialized cells, surrounded imperfectly with connective tissue, occupied the position in the sulcus terminalis conceded to be the locale of the S-A node, but, in addition, these cells extended almost completely around the orifice of the superior vena cava thus offering many more contacts to auricular muscle than the usually described node would possess.

3. A collection of these cells partially surrounded by connective tissue lies at the base of the interauricular septum just anterior to the mouth of the coronary sinus. Thus, we confirm the presence of an A-V node.

4. Several deep pathways unobstructed by connective tissue extend between the S-A and the A-V nodes. These pathways contain specialized cells and ordinary muscle cells.

5. From the A-V node somewhat parallel condensed strands of tissue pass through the membranous septum forming a structure identified as the Bundle of His.

6. The bundle ends by dividing into a broad, flat sheet of fibers on the left but in disagreement with many investigators we find more than one right branch. In addition, numerous septal connections from the main bundle and from its branches are reported.

7. Only one type of termination of this tissue is found, an end-to-end gradual transition into ordinary heart muscle.

8. Within the age space studied, there was more differentiation of specialized cells than of ordinary muscle cells.

9. The significance of these findings upon electrocardiographic interpretations is discussed.

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Abnormal Electrocardiograms in the Absence of Demonstrable Heart Disease

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APPARENT electrocardiographic abnormalities in the absence of heart disease have been reported with increasing frequency in recent years. With few exceptions, however, the divergences have been quantitative rather than qualitative. As an example, the normal limits of the P-R interval, QRS duration and axis deviation have been considerably extended without essentially distorting the normal pattern. However, abnormalities involving the ventricular component, particularly the T wave, have generally been considered pathologic and associated with disease of the heart. We are concerned in this paper with anomalies of the T wave, particularly the T wave derived from the thoracic leads, in patients in whom heart disease could not be proven.

Almost from the first, observers have been in accord regarding the direction of T waves obtained through the use of chest leads. However, because of the different technics employed these were variously described as normally inverted (earlier methods) and as normally erect (present technic). For example, Shipley and Halloran[16] published their observations on 200 normal men and women between the ages of twenty and thirty-five and noted inverted $T_{4,5}$ (old technic) in all. More recently Skulasen and Larsen[17] made a comparable study in the thirty to fifty year age group and found upright T waves in the chest leads (present methods, normal as taken).

In a group of 299 college students Wood, Wolferth and Miller[22] found three diphasic and one inverted $T_{4,5}$ the last in a young man with valvular heart disease. All the rest were erect.

More recently Graybiel et al.[3] made five lead electrocardiograms (limb leads, IVF and IVR) on 1,000 healthy young aviators and noted two diphasic T waves in IVF and none in IVR. No frankly inverted T waves were seen.

In a large study Edeiken, Wolferth and Wood[2] reported twenty-six instances of T_4 abnormality in adults demonstrating normal limb leads. However, all had some type of organic heart disease. The authors concluded that changes in the precordial leads should not be disregarded but should stimulate further search for evidence of heart disease. In their experience an upright T_4 (abnormal as taken) in an adult was never seen where "there was no significant disease of the heart."

However, apparently normal precordial T wave variants have been reported in the literature and in texts. Katz[7] states that the T wave in CF_2 is sometimes normally inverted in adolescents and rarely in young adults. Sodeman[18] described an abnormal T wave from the chest leads of a normal, healthy, twenty-four year old nurse without any evidence of heart disease.

Shanno[15] who made electrocardiographic studies in one hundred student nurses between the ages of eighteen and twenty-two found negative T waves six times in CF_2, once in CF_3 and not at all in CF_4. Neither Shanno nor Sodeman offered any explanation for these aberrations.

In 1943 Dupuy[1] published several grossly abnormal electrocardiograms from apparently healthy soldiers who did, however,

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have cardiovascular complaints which were considered to be functional. The T wave abnormalities appeared in all leads and could be reversed by rest and sedation.

Also in 1943 Thompson[19] described similar changes in certain susceptible individuals during hyperventilation. T wave abnormalities were seen in all leads in subjects with anxiety neuroses manifested by tachycardia, precordial pain and hyperventilation. The author expressed some uncertainty as to whether such individuals had perfectly normal hearts and considered the possibility that alkalosis resulting from hyperventilation caused further constriction of coronary vessels already altered to a subclinical degree.

In a recent communication based on electrocardiographic findings from 300 negro and 200 white normal adults, abnormal precordial T waves were noted in 4.6 per cent of the negroes and .5 per cent of the whites (one case).[11] Careful studies indicated that none of these people had organic disease of the heart. The aberrations were observed more frequently in negro women than in men, in individuals who had normal-sized or small hearts and who had a tendency to right axis deviation.

It was concluded that this represented a persistence of the juvenile form and was not a manifestation of organic heart disease. In support of this was the observation that the limb leads were all normal, that when the right arm was used as the indifferent electrode the T waves were commonly erect and finally that the precordial T waves tended to alter their direction with the passage of time.

Unfortunately, clinical studies on the direction of the T wave are of necessity on an empirical basis. Although it is truthfully stated that the T wave is coincident with restitution in the ventricles and the retreat of electrical activity, this merely constitutes a statement of fact and does not establish a causal relationship. In his textbook on electrocardiography Katz[7] suggests that the direction of the T wave is determined by the fact that the geometric pattern of restitution differs from the pattern during activation and prevents the electrical field during retreat from being opposite to that field during excitation. This is in agreement with observations that the base of the ventricles lags behind the apex during restitution and the right ventricle lags behind the left.

One of the most illuminating studies to date is that of Hoff, Nahum and Kisch[5] who were able to dissociate the ventricles by the use of potassium salts applied locally to the heart. They thus obtained pure dextro- and levo-cardiograms. These tracings were quite different from those derived from the intact, untreated heart and showed no trace of a T wave. However, the algebraic sum of the graphs derived separately from the left and right ventricles reconstituted the original normal tracing complete with T waves.

They concluded that the T wave resulted from interference of the terminal portions of the dextro- and levo-cardiograms. An upright T wave occurred when the dextrocardiogram was of greater duration than the levo-cardiogram, and an inverted T wave occurred when the opposite was true. By chilling the left ventricle and causing prolongation of the ventricular complex on the left side, a negative T wave was obtained.[4] Similar changes followed heating of the right ventricle. When the right ventricle was chilled or the left heated, the T wave became higher.

These observations are valid for limb leads and probably also for precordial electrocardiograms. In support of this experimental demonstration are the T wave changes resulting from chilling of the heart after the ingestion of ice water.[21]

Although the work of Nahum, Hoff and Kisch doubtless explains the T wave inversion noted in disease and injuries of the heart, it does not provide the answer to the inverted precordial T waves found in many children and some adults, particularly in those in whom the limb leads are normal. Earlier work by Katz and his associates[8,9,10] indicated that the nature and conductivity of the tissues immediately adjacent to the

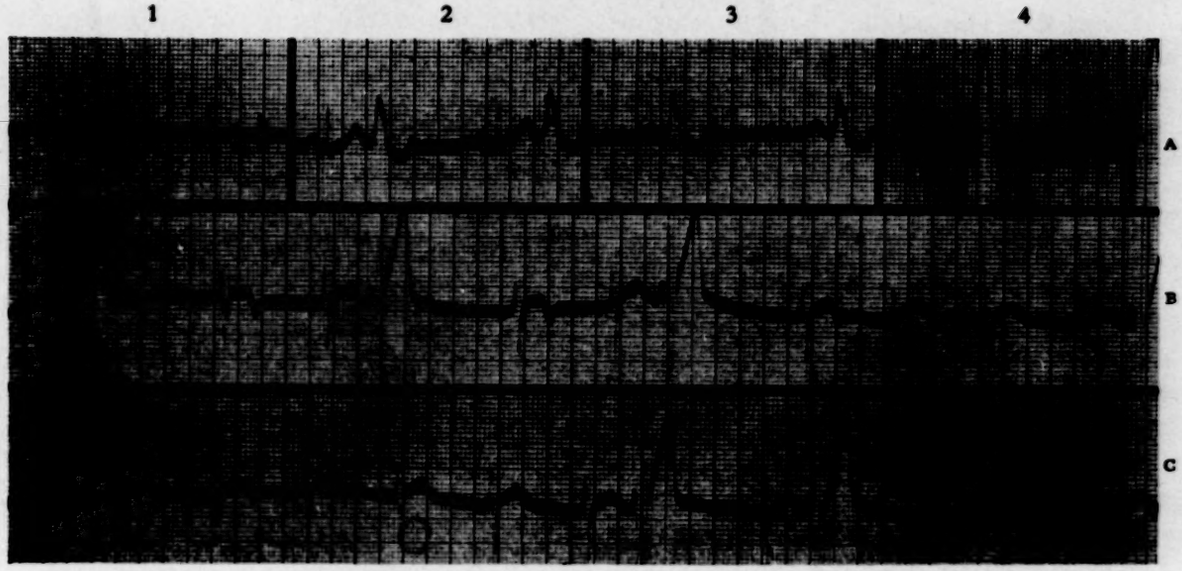

FIG. 1. Case I. A, obtained on admission; B and C, lead IVF, recorded three days later.

heart had a profound effect on the character of the electrocardiogram. Robinow, Katz and Bohning[13] who considered the problem of T_4 in children concluded that differences in the shape of the chest in juveniles as compared to adults accounted for much if not all of the character and direction of T_4 in children.

The cases to be described in this paper are intended to illustrate a group of anomalies largely concerned with precordial T waves in individuals without demonstrable heart disease. They were found over a period of approximately eighteen months during which time some 5,000 electrocardiograms were read. The high incidence is doubtless fortuitous since a much greater number of tracings had been observed earlier without a comparable number of similar anomalies. With one exception these individuals had no complaints referable to the heart. In that case the symptoms were considered to be due to a marked cardiac neurosis and aerophagia.

CASE REPORTS

CASE I. A twenty-nine year old white soldier was sent into the hospital from the separation center because of frequent extrasystoles. The patient was not aware of the arrhythmia and had no complaints referable to the heart. His previous health had always been good and the past history was non-contributory.

Physical examination revealed a well developed and nourished white man who was moderately nervous. The heart was not enlarged; the rate was 90 and numerous extrasystoles were noted. These were diminished but not abolished by exercise. A soft systolic murmur was heard in the beats succeeding the extrasystoles. The blood pressure was 120/70; temperature was normal; the sedimentation rate was 3 mm. per hour; the white blood count was 7,400; the urinalysis was normal and the Kahn test was negative. The basal metabolic rate was −4. The chest and heart were normal to radiography and fluoroscopy. Exercise tolerance was good.

The electrocardiogram revealed the presence of alternating ventricular premature beats. There was no important axis deviation and the ventricular components of the sinus beats in the limb leads were normal. In lead IVF the T waves of the sinus beats were sharply inverted. After several days during which no medication was given the patient became less nervous and fewer extrasystoles were noted. An electrocardiogram made at this time demonstrated T wave inversion only in the beats which followed the extrasystoles. Where a number of normal beats occurred in succession the first T wave was inverted, while those which followed were erect and quite within normal limits. With recurrence of the bigeminal rhythm the tracing resembled that made on admission. (Fig. 1.)

Comment. This soldier had no cardiac complaints, and unless extrasystoles are considered to be evidence of heart disease none could be demonstrated. To be sure, the T_4 abnormalities noted on the first tracing were alternating in character. However, where the only other beats present were ectopic in nature, the only conclusion which could be drawn was that T_4 was abnormal and possibly pathologic. Subsequently, when the extrasystoles became fewer in number, it became obvious that the anomaly occurred only following premature beats and was in some manner associated with them.

Recently Scherf[14] reported lowered and inverted T waves in various leads following extrasystoles. He considered that this probably indicated the presence of heart disease, particularly since it was noted only three times in the absence of cardiac illness. The mechanism was believed to be connected chiefly with changes in the filling of the heart.

In Case I alterations in cardiac filling were doubtless extensive. Considerable overdistention must have been present during the pause following the ectopic beats to account for the systolic murmur heard with each succeeding beat. How this was responsible for the T_4 inversion is not, however, plain. Any change in the coronary circulation could hardly have manifested itself so promptly or disappeared so soon.

CASE II. A twenty-six year old white officer was seen in consultation because of a cardiac murmur which was said to have been heard from time to time. Otherwise the history was entirely unremarkable. There were no cardiac or other complaints of any sort.

He was a tall, slim young man who appeared neither acutely nor chronically ill. Except for a moderate funnel deformity of the chest the examination revealed nothing abnormal. The heart was not enlarged, the rate was moderate and the rhythm was regular. The first sound at the apex was impure and the second sound was occasionally reduplicated. No murmurs were heard and no thrills were felt. The blood pressure was 122/78.

Urinalysis was negative, the white blood count was 5,900, hemoglobin 90 per cent, sedimentation rate 2 mm. per hour and the serology was negative. The temperature was normal. X-ray of the chest showed the heart to be of normal contour with a transverse diameter of 12.8 cm., exactly average according to the tables of Ungerleider and Gubner.[20] All of the cardiac function studies were within normal limits.

The electrocardiogram showed a sharply inverted T wave in CF_2, a lesser inversion in CF_3 and an erect wave in CF_4. The CR leads all had erect T waves. Repeated tracings over a period of one month remained unaltered.

CASE III. This twenty-three year old negro soldier was one of a group of normal young people selected as subjects for an electrocardiographic survey. He had no complaints of any sort, used no drugs and had never been seriously ill.

He was 69 inches tall and weighed 140 pounds. The heart was entirely normal to physical examination and his exercise tolerance was excellent. Blood pressure was 120/82. According to the Ungerleider and Gubner tables[20] his heart size by radiography was 9 per cent below average normal. Hemoglobin was 104 per cent, the white blood count 7,600 and the erythrocyte sedimentation rate was 4 mm. per hour.

The electrocardiogram showed essentially normal limb leads and axis deviation. The T waves in $CF_{2,3,4,5\text{ and }6}$ (5 and 6 not shown) demonstrated varying degrees of inversion. The T_{CR} waves, however, were erect and normal. Two other tracings made over a one-month period was unchanged.

Comment on Cases II *and* III. These two cases were considered to represent persistence of the juvenile pattern in the electrocardiogram of adults. (Fig. 2.) The study of negroes and whites noted earlier[11] indicated that a significant number of negroes retained the juvenile configuration of the chest leads into maturity. The incidence of this phenomenon was very much smaller in whites but it did occur. Careful study of these individuals indicated that this constituted a normal variant and was not the result of myocardial disease.

Katz[7] in his textbook on electrocardiography states that the T wave in CF_2 is

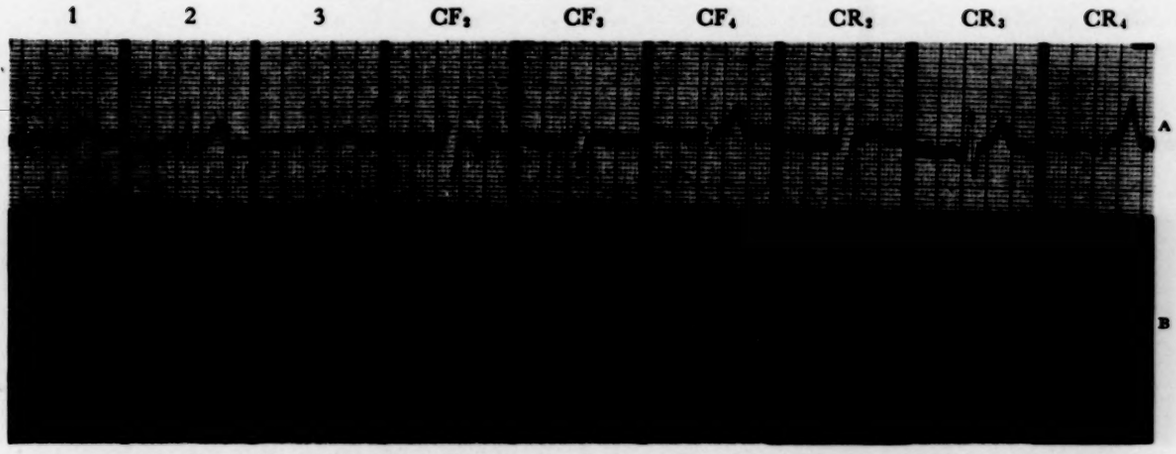

FIG. 2. Examples of juvenile electrocardiograms in adults; A, Case II; B, Case III.

occasionally diphasic or inverted in normal young adults. In Case II this inversion was present also in CF_3 while in Case III it persisted all the way to CF_6.

The electrocardiographic pattern of youth is rather characteristic and not easily confused with other similar deviants.[12] The limb leads are ordinarily entirely normal but may show slight degrees of right axis deviation. The T waves may be diphasic or inverted from CF_2 all the way through CF_6 but are generally inverted only in the leads nearest the sternum, CF_2, CF_3 and occasionally CF_4. T wave inversion is never seen in CF_4 or CF_5 without equivalent or greater inversion in CF_2 and CF_3. TCR_2 is very rarely diphasic or inverted but is usually erect. The T wave was not observed to be inverted in the other CR positions.

T wave inversion in chest leads of children is thought to be the result of a tendency to right axis deviation and to a difference in the configuration of the puerile chest as compared to that of the adult.[13] However, such a difference could not be demonstrated in these cases.

CASE IV. This twenty-six year old white soldier was one of a group of normal individuals on whom an electrocardiographic survey was made. He had no cardiac complaints of any sort and had never been seriously ill. He was a well developed and somewhat obese young man and the physical examination was entirely normal. The heart was not enlarged to percussion, the rate was moderate and the rhythm was regular. No murmurs were heard and no thrills were felt. The blood pressure was 128/84. Exercise tolerance was excellent.

The urinalysis, blood counts, hemoglobin, erythrocyte sedimentation rate and serology were all normal. X-ray of the chest demonstrated a heart which was somewhat transversely placed but which was not enlarged or distorted. The lungs were normal.

The first electrocardiogram obtained demonstrated left axis deviation, low amplitude of T waves generally, questionably diphasic T_2 and inverted T_3. The T in CF_2 was small and multiphasic; it was slightly but definitely inverted in CF_3 and CF_4 and in CR_2, CR_3 and CR_4.

One month later there was no significant change in the limb leads but the T wave inversion in the chest leads had become exaggerated and involved CF_2 which previously had been mostly upright. The greatest inversion was noted in CF_3 and in CR_3.

After a lapse of one more month an electrocardiogram demonstrated significant increase in the height of T_2 while T_3 was more deeply inverted. All of the waves from the thoracic leads had become erect although they still were somewhat low. (Fig. 3.)

Throughout this period of observation there were no complaints referable to the heart and no evidence of infection or inflammation.

CASE V. A twenty-two year old white soldier who had completed three years of service was sent into the hospital because of cardiac arrhythmia and a murmur. He had no complaints of any sort. Until the age of nine he was said to have had some sort of fever each summer (possibly malaria) but never had scarlet fever or rheumatic fever. At the age of six he was

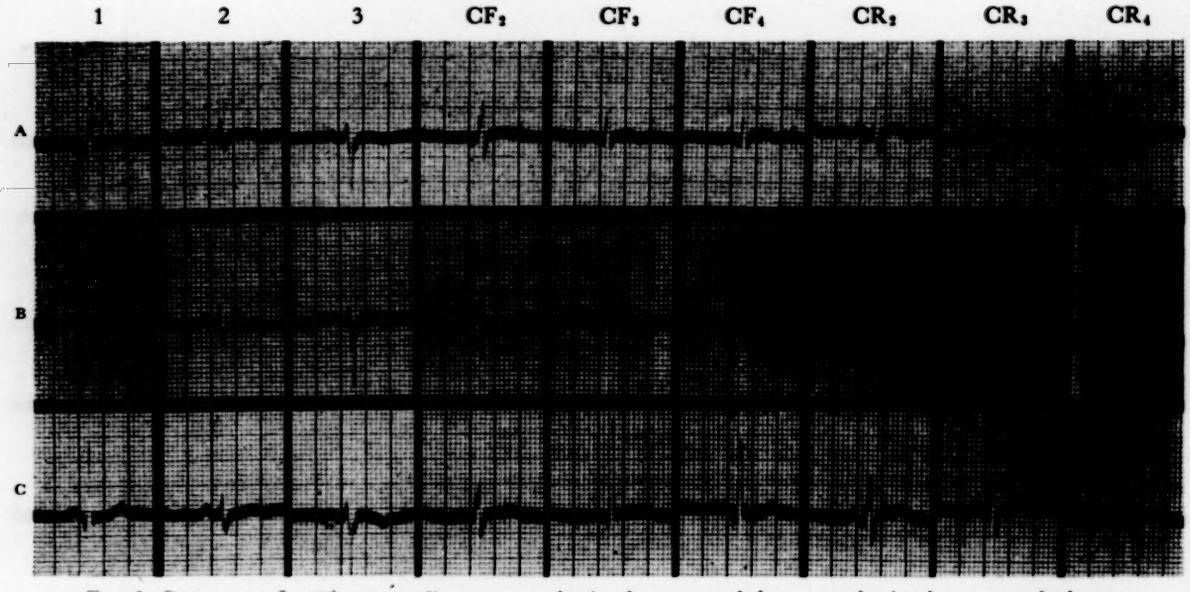

FIG. 3. Case IV. A, first electrocardiogram; B, obtained one month later; C, obtained two months later.

injured in a dynamite blast which destroyed the sight of the right eye. Shortly before coming into the army he had an appendectomy.

Physical examination revealed a well developed and nourished young man who did not appear ill. There was a large corneal opacity of the right eye. The heart was not enlarged to percussion. The rate was 76 and there was a marked sinus arrhythmia. A very soft systolic murmur was localized over the apex. No other murmurs were heard and no thrills were felt. The blood pressure was 128/76. All of the reflexes were normal and the examination was otherwise entirely unremarkable. Exercise tolerance was excellent.

The urine was normal, serology negative, white blood count 8,200 and the sedimentation rate was 8 mm. per hour. X-ray of the chest revealed a heart which was neither enlarged nor distorted. Fluoroscopy added no further information.

An electrocardiogram made shortly after admission to the hospital showed marked sinus arrhythmia. The axis was vertical and T_1 was somewhat low. The T wave in CF_2 was upright, it was inverted in CF_3 and CF_4, upright in CR_2 and diphasic in CR_3 and CR_4. Three days later there was no significant change in the limb leads nor were changes seen in these leads at any time subsequently. TCF_3, however, had become diphasic and TCF_4 was inverted to a lesser degree than formerly. TCR_3 had become more negative than before.

Approximately one week after his admission to the hospital a complete tracing demonstrated upright and adequate T waves in all of the CF and CR leads. A few days later inversions were again apparent and this time negative elements were present in the T waves of CF_2 and CR_2 which had previously been entirely upright. The last tracing taken several days later showed only a diphasic TCF_3 and TCF_4. (Fig. 4.)

Occasionally varying degrees of T wave inversion could be seen in successive beats of the same tracing. When this happened, the greatest degree of T wave inversion was seen in the beats which followed the longest pauses during the course of the sinus arrhythmia.

During the period of observation this patient had no complaints nor did he manifest any evidence of infection or inflammation. The temperature was continuously flat and the white blood count and sedimentation rate did not vary significantly from those obtained on admission.

CASE VI. An eighteen year old white soldier was seen at the cardiac clinic at the request of his commanding officer for the purpose of determining whether he should be retained in a limited service capacity because of heart disease. As a child he is said to have had a murmur which was observed over a period of years by his family physician. Directly after coming into the army he was hospitalized because of his history and later placed on a limited service status. The patient knew that he had "heart disease" but was exceedingly vague as to symptoms. Although there were no complaints

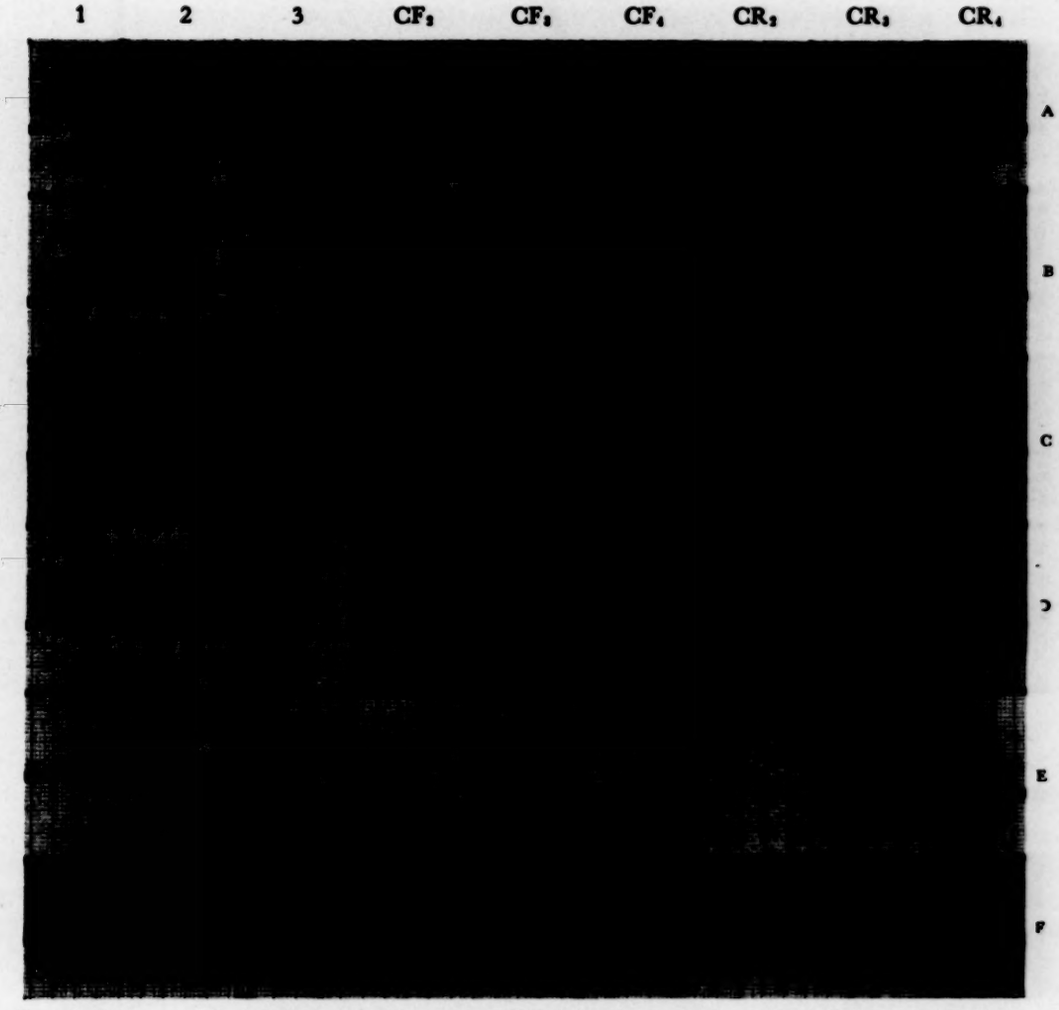

FIG. 4. Case V. A, obtained on admission; B, recorded three days later; C, recorded seven days later; D, recorded ten days later; E, recorded fourteen days later; F, lead CF_3 made at same time as D above.

directly referable to the heart, he had an active cardiac awareness and neurosis.

Physical examination revealed a well developed and nourished young man who did not appear acutely or chronically ill. The head and neck were normal and there were no abnormal cervical pulsations. The chest was symmetrical and the lungs were clear. The heart was not enlarged, the rate was 70 per minute and the rhythm was regular. The sounds were good and no murmurs or thrills were noted. The blood pressure was 110/68. The abdomen, extremities and reflexes were all normal. Exercise tolerance was excellent.

The urine was normal, the serology negative and blood counts, hemoglobin and sedimentation rates were all well within normal limits. The temperature was flat at all times and there was no evidence of infection or inflammation.

A complete electrocardiogram was made shortly after admission which showed sino-auricular rhythm and a normal axis. T_1 was inverted and T_2 was very small and multiphasic. T_{CF_2} was normal; T_{CF_3} was diphasic and T_{CF_4} and $_5$ were inverted. Similar changes were seen in the T waves of the CR and CL leads.

Repeated tracings over a period of time showed no significant changes from the one made originally. However, following very vigorous exercise a curve could be regularly obtained which was quite within normal limits. (Fig. 5.) T_1 and T_2 would then appear upright and were of normal amplitude. Leads CF_4 and CF_5 which generally showed the greatest degree of T wave inversion acquired T waves which although somewhat low were upright and essentially normal.

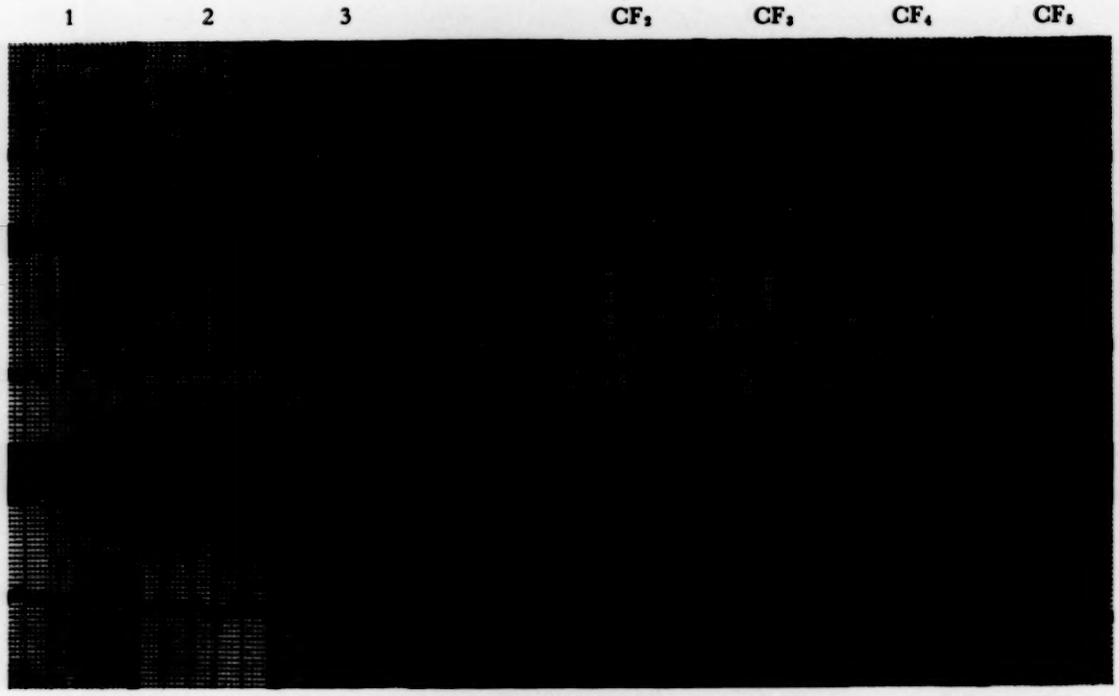

FIG. 5. Case IV. Upper tracing as indicated obtained on admission; lower tracing record following vigorous exercise.

CASE VII. A twenty-two year old white man was admitted to the hospital with a diagnosis of chronic pericarditis. He had no complaints. Two years earlier while in the armed forces he awoke one morning with an indistinct, dull pain in the chest which was made worse by deep breathing. He was subsequently hospitalized and studied for ten weeks. The pain persisted for approximately ten days but was unassociated with fever, chills, cough or feeling of illness. Eventually he received a medical discharge for what is said to have been chronic pericarditis. The earlier history was non-contributory.

Upon his return to civilian life he did nothing for some months. Later he was examined at a Veterans Hospital and advised to return to work as no evidence of disease was present. He did this but after two weeks he became aware of retrosternal discomfort and was admitted to another Veterans Hospital for study.

Physical examination revealed a well developed and nourished young man who did not appear ill. The heart was not enlarged, the rate was moderate and the rhythm was regular. The sounds were excellent and no murmurs or other adventitious sounds were heard. The blood pressure was 110/80. There was no increase of the venous pressure, no edema and no ascites. The lungs were clear and no abdominal organs were felt. The white blood count was 6,300 and the sedimentation rate was 5 mm. per hour. All other laboratory studies were entirely within normal limits. Throughout the period of observation the temperature was normal and there were no complaints or indications of active disease of any character.

X-ray of the chest revealed normal lung fields and a heart which was normally placed and neither enlarged nor distorted. Fluoroscopy revealed no evidence of individual chamber enlargement and the cardiac pulsation was ample and unhibited.

The electrocardiogram on admission was grossly abnormal. T wave inversion was apparent in L_I, L_{II}, CF_2, CF_3, CF_4 and in CR_2, CR_3 and CR_4. The QRS complex, however, was not remarkable and there were no significant deviations of the S-T segments.

Subsequently tracings were made under various conditions in an effort to determine the validity and constancy of the findings. They were obtained before and after exercise, the administration of atropine and of prostigmine, breathing of 100 per cent and of 10 per cent oxygen, on an empty stomach, a full stomach and in various positions. Regardless of the conditions imposed the electrocardiogram remained unchanged and abnormal until a con-

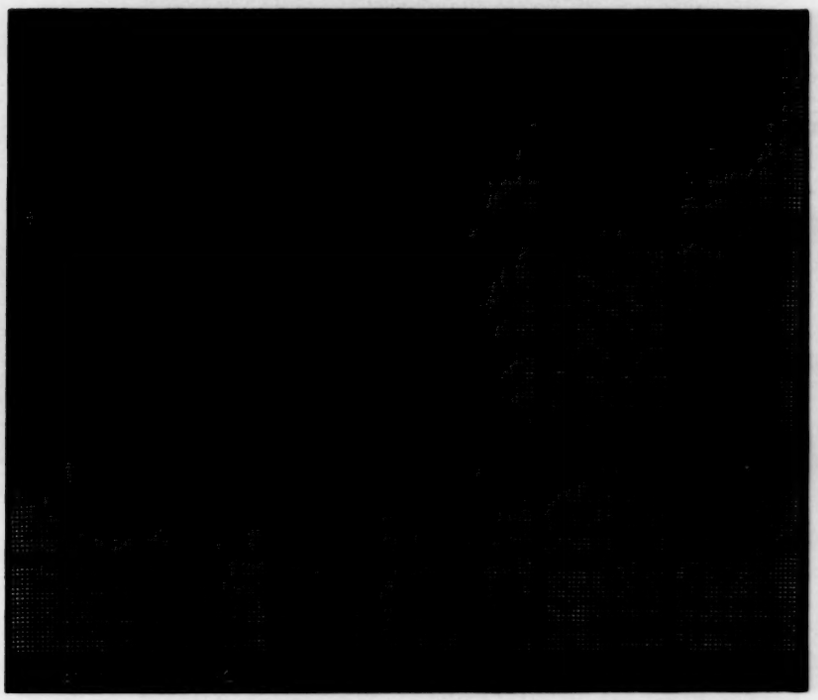

FIG. 6. Case VII. A, obtained on admission; B, spontaneous reversion to normal.

trol tracing was made prior to the administration of 100 per cent oxygen. This occurred some two weeks after his admission to the hospital. This curve showed diphasic-to-upright T waves in the limb leads and in CF_4 while TCF_2 was frankly upright. No additional changes occurred after breathing 100 per cent oxygen. Two days later the tracing became entirely normal and has remained so. (Fig. 6.) It must be emphasized that during the period of observation there was no change in the laboratory findings or in subjective sensations.

Eventually the patient was released after being told that there was no evidence of heart disease and advised to return to work. He was instructed to return at stated intervals for additional examinations.

Comment on Cases IV, V, VI *and* VII. These cases are grouped together because of their several common features. The limb leads contained T wave deviations which varied from lowering and flattening to frank inversion. The most spectacular abnormalities, however, were noted in the thoracic leads. The greatest degree of inversion of the T wave occurred at or near the apical position. In this respect they differed from Cases II and III in which the points of greatest T wave negativity were at or near the sternal border and then only in the CF leads. The QRS complex and S-T segments were normal. In all these subjects essentially normal curves were obtained with the passage of time or following vigorous exercise.

The possibility of obscure but real myocardial disease in these individuals cannot be overlooked. Although the first patient was never aware of any illness, the second had a series of conditions any of which might have resulted in organic changes in the heart. The third is said to have had a murmur in childhood while the last patient must certainly have had something abnormal to result in ten weeks' confinement in an army hospital. The record is not clear on this point, however, and the abnormality may well have been confined to the electrocardiographic findings.

In spite of the possibility that organic changes might be present in these individuals, no diagnostic means at present available served to substantiate this claim. It will be recalled that in none of the patients at present under discussion was there any alteration in laboratory or x-ray findings nor were there any unusual physical

findings. We have here the curious phenomenon of abnormal electrocardiograms which righted themselves following the passage of time (days to weeks) or after vigorous exercise in the absence of any evidence of disease activity.

If we can discount the possibility of associated organic changes, and this seems reasonable, the mechanism of the unstable T wave, although obscure, becomes susceptible of analysis. Hoff, Nahum and Kisch[5] who made experimental studies of the T wave concluded that the direction of this portion of the electrocardiogram was dependent upon slight but constant asynchrony of the terminal electrical phenomena of the ventricles. Organic or functional delay in that portion of the electrocardiogram derived from the left ventricle led to inversion of the T wave; the same change also resulted from shortening of the right side. One may be forgiven perhaps for postulating that some normal hearts do not possess the same degree of ventricular asynchronism but instead exhibit an unstable equilibrium manifested by varying direction of the T wave. This could be the result from minute changes in synchronism such as might in other normal hearts merely cause slight lowering or heightening of the T wave. Another possibility to be considered is that some normal individuals are possessed of an unusually labile or exaggerated asynchronism of the terminal portion of the ventricular complex leading to the same result. For example, the T wave inversion obtained by means of ice water ingestion occurs much more promptly in some subjects than in others and cannot be performed at all in some individuals.

It is suggested that these patients represent instances of normal hearts with normally unstable T waves.

Case VIII. A twenty-three year old white soldier who had completed four years of army service was sent into the hospital from the separation center because of a complaint of shortness of breath and rapid beating of the heart. At the age of seven he had pneumonia and this occurred again when he was fourteen. When he was eighteen years old he is said to have had mumps which was then followed by some type of heart condition. He was given digitalis for this and took the drug until his enlistment in the army when he stopped the medication. He went through several campaigns and served vigorously and without difficulty until approximately three months before his discharge. At this time he became aware of precordial discomfort, shortness of breath and rapid heart action. During the same interval he lost approximately 15 pounds.

Examination revealed a very well developed and nourished young man who exhibited sighing respiration but who otherwise did not appear ill. His head and neck were normal. The chest was symmetrical and the lungs clear. The heart was not enlarged, the rate was moderate and the rhythm regular. The sounds were of good quality and no murmurs or thrills were noted.

Several urinalyses showed good concentration and were free of albumen and sugar. The hemoglobin was 104 per cent, the white blood count 8,450 and the sedimentation rate 4 mm. per hour. The basal metabolism was −7 and the serology was negative. X-ray of the chest demonstrated normal lung fields and a heart which was not enlarged. Fluoroscopy added no further information. A gastric analysis was normal and a gastrointestinal series was negative except for the demonstration of a cascade stomach and a high splenic flexure. All cardiac function studies were normal.

The first electrocardiogram made shortly after admission demonstrated normal limb leads with sinus rhythm and normal axis. T wave inversion was apparent in CF_2, CF_3, CF_4, CR_2 and in CR_3. One morning several days after admission the patient was sedated with 3 gr. of seconal and an electrocardiogram made while he was asleep. This curve was entirely normal in all leads. Accordingly, an attempt was made to duplicate this result by the use of hypnosis. This was done the following afternoon but the tracing obtained was abnormal and identical in appearance to that made on admission. At this time a dose of seconal was administered and when this had become effective another tracing was made. However, this one also was abnormal.

The following day a complete electrocardiogram was made before the patient got out of bed. He was then sedated and another curve obtained. At this time it was noted that the tracings made before sedation and after sedation

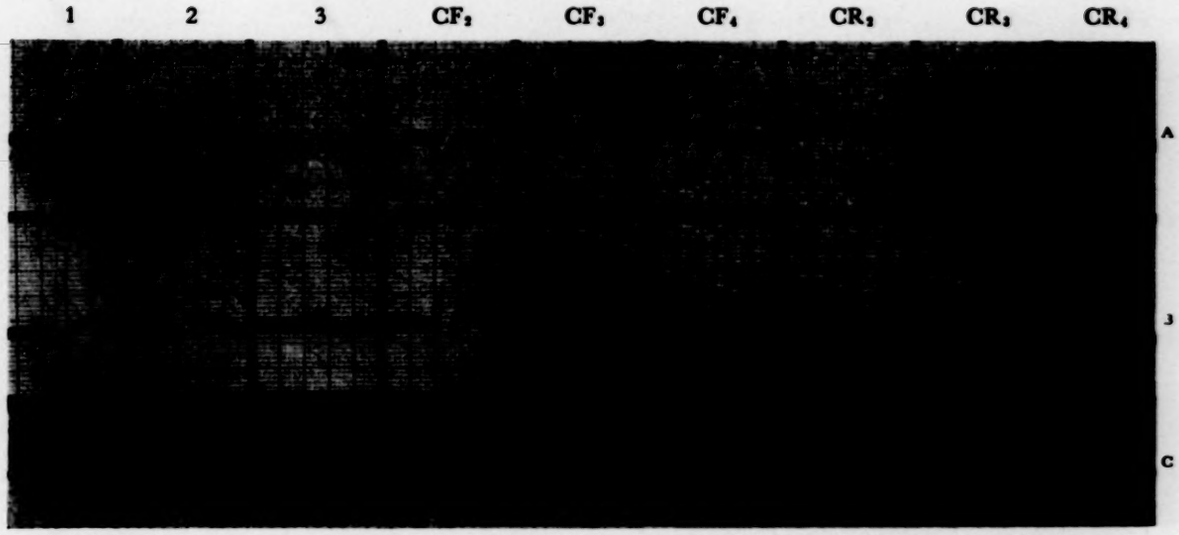

FIG. 7. Case VIII. A, obtained on admission and thereafter in the afternoon; B, obtained before eating in the morning; C, continuous IVF tracing obtained before and during inflation of the stomach. Injection of air began with the second beat.

were both normal. It later became apparent that the curves obtained in the morning before the patient had eaten were normal while those made later in the day appeared abnormal and pathologic. No significant changes were observed following exercise, hyperventilation or the administration of atropine or prostigmine.

On several occasions the stomach was completely evacuated in the morning and then distended with air. A continuous curve made during this procedure demonstrated first depression then inversion of the T wave while the stomach was inflated. Before the air was injected and after it was removed the curve was normal. (Fig. 7.)

Comment. It is entirely possible that this patient had some degree of myocarditis following his attack of mumps four years earlier. However, it is doubtful if this could have produced changes later manifested by changes in the electrocardiogram during distention of the stomach. There was no evidence of heart disease by physical examination, x-ray or any other diagnostic procedure. The sighing respiration was believed to be due to a very active cardiac neurosis and was not present when the patient was reading or occupied with other diversions. Much of the gastric distention was thought to be the result of air swallowing.

It appears likely that the electrocardiographic anomalies in this case were in some manner associated with the state of filling of the stomach and possibly the colon. The exact modus operandi, however, is obscure. It is doubtful if the physical presence of air or food in the stomach could result in the changes noted. On the other hand, such effects could conceivably result through retrograde stimulation of the vagus or sympathetic systems. However, the administration of atropine and of prostigmine produced no significant alteration of the curve.

CASE IX. An eighteen year old white soldier was sent to the hospital with a diagnosis of coronary thrombosis and a complaint of severe substernal pain which radiated to the neck and shoulders. This occurred some two hours earlier without physical strain while he was seated at a desk. He felt somewhat more comfortable in the erect position than when recumbent. The past history was entirely non-contributory.

The patient was pale and sweating when first seen and in slight shock. The temperature was 97.8°F., the pulse 96 per minute and the blood pressure 120/76. Due to his condition the examination was carried out in the supine position. The lungs were apparently normal and the heart was remarkable only in that percussion was unsatisfactory and the sounds were distant.

An electrocardiogram made shortly after admission demonstrated a low T_1, an absent R_4 and a slightly inverted T_4 (IVF). At this time

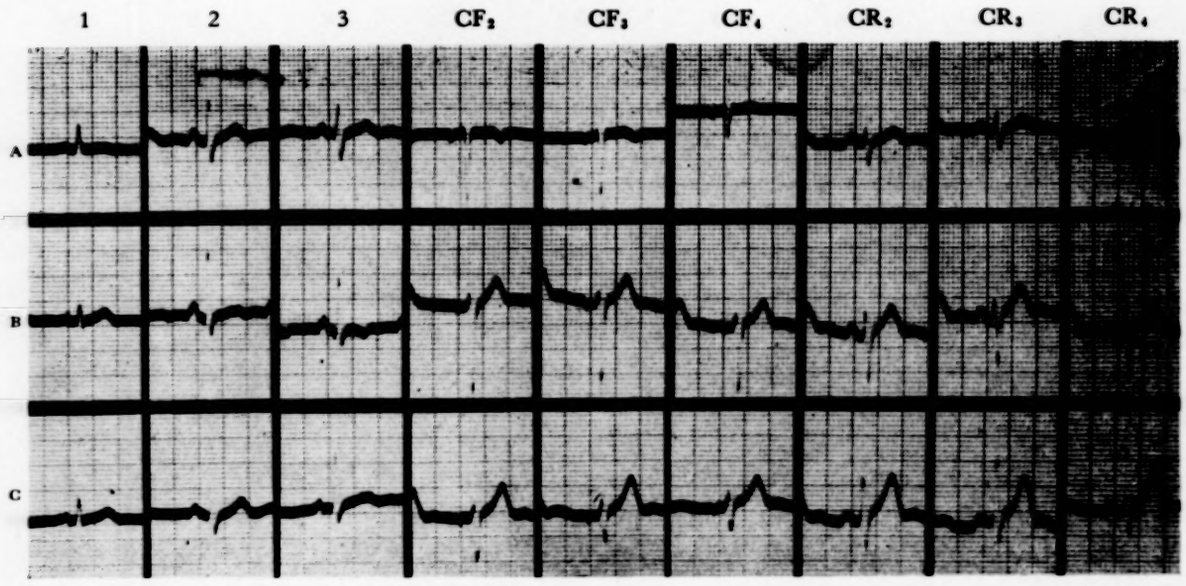

FIG. 8. Case IX. A, obtained on admission in the supine position; B, recorded at the same time in the upright position; C, recorded after recovery in the supine position.

the patient was reexamined in the erect position and Hamman's sign was at once apparent; the heart sounds were louder and the left cardiac border could be percussed without difficulty. An x-ray of the chest confirmed the impression of spontaneous pneumothorax on the left with approximately 10 per cent collapse. Lateral radiographs demonstrated air in the mediastinum.

Additional electrocardiograms were made including CF_2, CF_3, CF_4, CR_2, CR_3 and CR_4 in the supine, prone and erect positions. The CF leads made in the supine position showed small to absent R waves and flat to inverted T waves. In the erect and prone positions the T waves in all the CF leads became erect although the R waves remained small. T_1 which had previously been very low became of normal amplitude and T_3 became inverted. The T waves derived from the CR leads were somewhat lower in the supine position than in the erect. However, the CR leads were within the normal range in any position. (Fig. 8.)

When the mediastinal emphysema and the pneumothorax had cleared the tracing became normal in all leads and in all positions. It was then essentially similar to the curve obtained originally in the erect position. The R waves in the CF leads remained small.

Comment. The T wave inversion in this case resembled that found in children and in Cases II and III described earlier. The greatest degree of inversion was present in CF_2 while the CR leads were normal. The cause for this phenomenon was doubtless the physical presence of air in the mediastinum and in the pleural space lying between the heart and the chest wall on the left. This produced a region of diminished conductivity and interfered with the normal inscription of the electrocardiogram. When the patient was in the erect or prone position and air was no longer trapped between the heart and the exploring electrode, part of the non-conducting medium was removed and the tracing became essentially normal. This is in complete accord with the experimental demonstrations of Katz and his associates[8] who concluded that "alterations in the relation of various regions of the heart to the good electrical conductors and alterations in the location of the latter are important factors in modifying the ordinary electrocardiogram."

The interference phenomenon was apparently less important when the right arm was used as the indifferent electrode than the left leg. The reason for this is not readily apparent but must be associated with the different pathways normally utilized to complete the electrical circuit in the various leads.

COMMENTS

The cases presented in this study have demonstrated the fact that at one time or another they all exhibited grossly abnormal electrocardiograms without heart disease that could be otherwise proven. The cause for the abnormalities was apparent in some and quite obscure in others. Where it could be determined that the T wave inversion was the result of spontaneous pneumothorax with mediastinal emphysema or constituted persistence of the juvenile pattern, the diagnosis was neither sinister nor difficult to make. On the other hand, in the other cases presented no definite diagnosis could be made or sustained. It is impossible to state at this time that they did not represent instances of preclinical heart disease which will become manifest with the passage of time. Nevertheless, with the exception of the electrocardiogram it was impossible to make a diagnosis of organic heart disease by physical examination or by any other means now at our disposal.

It then becomes a question whether the unsupported inscription of the electrical phenomena of the heart as interpreted by present methods can be implicitly depended upon to make a diagnosis of heart disease or whether it should be treated as merely one diagnostic procedure to be integrated with other findings. In view of the fact that our electrocardiographic limits of normal have been constantly expanded it seems safer at this time to reserve the diagnosis of organic disease of the heart for those cases in which the condition can be proven by additional means. Doubtless, at some time in the future the limits of normal will be more clearly defined and additional refinements of technic will have been made so that electrocardiographic findings will carry greater diagnostic weight.

This is suggested in those cases considered to represent persistence of the juvenile pattern. In these individuals abnormalities were present only in the CF leads while the CR leads were normal. In a similar manner the case of spontaneous pneumothorax demonstrated abnormalities limited to the CF leads and then only when made in the supine position. Additionally, the value of serial tracings is emphasized. It will be recalled that with few exceptions it was possible to obtain essentially normal curves after the passage of time following exercise or when made on an empty stomach.

Accordingly, when abnormal curves are encountered without adequate support of additional findings, the following extensions of electrocardiographic technic are recommended: (1) Electrocardiograms made with multiple chest leads employing the several standard indifferent points;[6] (2) tracings recorded with the patient in various positions; (3) tracings made at various hours of the day, before and after meals; (4) curves obtained before and after exercise and (5) serial tracings made over a period of weeks or months.

It is entirely probable that a carefully individualized approach may serve to demonstrate normal curves in many subjects having functional or non-cardiac electrocardiographic anomalies.

SUMMARY AND CONCLUSIONS

Nine instances of gross electrocardiographic abnormalities are described in individuals without demonstrable disease of the heart. The deviations were greatest in the thoracic leads.

Essentially normal curves were eventually obtained in most of the subjects by various means.

The cause for the anomalies was demonstrated in several of the patients but remained obscure in the remainder.

It is suggested that refinements in electrocardiographic technic may serve to demonstrate normal electrocardiograms when ordinary methods indicate a state of disease.

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Asymptomatic Heart Disease*

Observations Made during the Early Recruiting Period for Navy and Marine Enlistments

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THE opportunity of investigating cardiovascular disease entirely free from the elaborate overemphasis of a patient's subjective symptomatology is, unfortunately, not common. Individuals only come to a cardiac clinic or to a doctor's office for relief of subjective complaints; occasionally, unsuspected heart disease is discovered in patients being examined for other conditions. Applicants for life insurance are sometimes found with asymptomatic cardiovascular disturbances but no large groups of such patients are encountered in private or hospital practice.

This report is concerned with a special group of asymptomatic men and boys, all with one type of cardiovascular disease or another, who were discovered during the enlistment examination for admission into the Navy or Marine Corps during the early months of the recruiting period following Pearl Harbor. From December 8, 1941 until July 15, 1942, about 1,900 candidates were referred from the recruiting offices to the cardiac service of a certain naval hospital for diagnosis; of these, 350 were selected for special study because they were without symptoms or subjective complaints of any kind. As a by product of the mobilization of man power for war this group of individuals with asymptomatic heart disease seemed worthy of special investigation.

It must be admitted at the very outset that the choice of these patients for study was accomplished with some difficulty and only after considerable individual questioning. The patriotic appeal for enlistment after the Pearl Harbor disaster swept into every recruiting office tens of thousands of youths and older men, all anxious to get into the Navy or Marine Corps. Many knew that they had disabilities of one kind or another but each one cherished the hope that he might, however, be accepted. This led naturally to the denial of previous medical conditions and to convenient memory lapses in regard to anything in the past history which could be considered disqualifying. When such disabilities were subsequently discovered on physical examination, most of the candidates goodnaturedly admitted the discrepancies in their stories and said that it was only the desire to serve their country that caused them to make mis-statements.

There was a large group of candidates for enlistment, roughly about one-eighth of the total, who expressed surprise upon being told that they were unable to pass the general physical examination. Many of them were sent to the various special clinics for more intensive study and diagnosis as well as for evaluation of discovered defects. The cardiovascular service, as indicated before, received about 1,900 of these individuals. A simple breakdown of the figures shows that about one-half (825) denied knowledge of previous cardiovascular conditions; of these, 243 finally admitted a history of rheumatic fever either

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by name or symptoms (growing pains, St. Vitus dance, acute arthritis, heart fever) and 188 on close questioning confessed to either present or past symptoms of myocardial insufficiency (dyspnea, palpitation, heart pain or congestive failure). The remaining 394 individuals were again screened from the point of view of honesty, reliability and cooperativeness; forty-four were rejected, leaving the group of 350 which forms the basis of this report.

The ages of these candidates covered the years between seventeen and fifty-one; the general average was twenty-six. The largest group was in the twenty-three year class; the smallest in the forty-seven, forty-nine, fifty and fifty-one year classes which had three each. Of the 350 selected for the study, 336 were white, twelve were negroes and there was one American Indian and one Chinaman. As a group they represented a cross section of men in the average American city; nearly every trade, profession and type of work was found in the statistical data and the educational background was higher than the general population index. All but fifty-four were high school graduates and of these only twelve had less than two years of secondary school education. These latter facts are mentioned only to suggest that the group as a whole was intelligent and understanding; this background is necessary in giving the proper evaluation to their previous history and absence of cardiovascular symptoms.

A summary of the five general disturbances of the heart and blood vessel system which were found in this asymptomatic group is presented in Table I.

The distribution of these conditions is interesting; the number of cardiac irregularities is high compared with the incidence of arteriosclerosis. It is no surprise to find that arteriosclerosis may be productive of no symptoms; patients with advanced vascular degenerative changes may be entirely symptom-free. Irregularities of the heart, on the other hand, are frequently associated with considerable cardiac consciousness, sometimes out of proportion to the actual hemodynamic disturbance created, for example, by premature contractions. Valvular heart disease and hypertension account for more than one-half of the disabilities found and simple cardiac hypertrophy for about 7 per cent of these asymptomatic patients. It may be profitable to consider each of the five major groups in some greater detail.

TABLE I
CARDIOVASCULAR CONDITIONS FOUND IN ASYMPTOMATIC GROUP

Valvular heart disease	169
Hypertension	89
Irregularities of the heart	55
Simple hypertrophy	26
Arteriosclerosis (premature)	11
Total	350

VALVULAR HEART DISEASE

Valvular heart disease is ordinarily associated with a symptom complex which is well embroidered with a number of subjective complaints, both great and small. While the various valve disorders have more or less specific and characteristic symptoms, there are certain complaints common to all. Heart pain and heart consciousness are the most frequent while the patient is at rest; palpitation and dyspnea occur after exercise.

The relative distribution of the valve lesions found in this asymptomatic group is shown in Table II. In most of the patients the pathologic condition was chiefly localized to one valve but in those instances in which more than one murmur was heard only the predominating lesion was given.

Mitral Insufficiency. In the group of candidates with mitral insufficiency six had hearts graded as greatly increased in size by x-ray mensuration, fourteen moderately enlarged and nineteen slightly enlarged; the remaining fifty-four had hearts of normal size. The murmurs received the following grades: sixteen candidates had grade 4 murmurs, thirty-two had grade 3, twenty had grade 2 and twenty-five grade 1. There was no relationship between loudness, intensity and distribution of the systolic

murmur compared to the size of the heart. Three men with grade 1 murmurs had the largest hearts and eleven with grade 4 murmurs had normal-sized hearts. Of the six patients with greatly enlarged hearts only three had a left axis deviation by electrocardiographic examination; the fourteen with moderately enlarged hearts showed but one left axis deviation. The group of nineteen with slightly enlarged hearts showed three left axis deviations and the remaining fifty-four normal-sized hearts had two left and five right axis deviations.

TABLE II
DISTRIBUTION OF VALVE LESIONS

Mitral insufficiency	93
Mitral stenosis	41
Aortic insufficiency	22
Aortic stenosis	9
Congenital lesions	4
Total	169

No correlation curves could be established either between the length of the P-R interval and the size of the heart or the grading of the murmur. All possible combinations of these three factors were discovered. Abnormally long P-R intervals up to 0.28 second were found in grade 1 murmurs and normal-sized hearts; all of the patients with grade 4 murmurs and enlarged hearts had a P-R interval under 0.20 second. Finally, no relationship was found in regard to the standard exercise tolerance test with either the grading or the murmur, size of the heart or ECG changes. Candidates with the largest hearts and loudest murmurs seemed to do about as well as those with normal-sized hearts and grade 1 murmurs; in fact, the poorest showing in the test was made by seven youths all with grade 1 murmurs and normal sized hearts.

In summary, it would appear that in patients with asymptomatic mitral insufficiency no obvious relationship exists between (1) loudness, duration and distribution of the systolic murmur; (2) size of the heart; (3) electrocardiographic changes and (4) the exercise tolerance test. Statistically, this lesion was the most common valvular disease and it accounted for more than one-half of all the murmurs discovered; it was more than twice as frequent as mitral stenosis, four times more frequent than aortic insufficiency and ten times more common than aortic stenosis.

Mitral Stenosis. Forty-one of the 350 candidates studied had presystolic murmurs; this is about 12 per cent of the whole group and 25 per cent of those with valvular lesions. Those with presystolic murmurs received the following grades: five individuals had a grade 1 murmur, twenty-two had grade 2, eight had grade 3 and six grade 4. X-ray mensuration showed that twenty-six had no change in heart size, five had a slight increase, six a moderate increase and four had greatly enlarged hearts. ECG studies showed eight patients with P-R intervals longer than 0.20 second, six with simple right axis deviation, ten with a combination of P-R delay, axis deviation and other abnormalities like a QRS spread beyond 0.12 second, S-T changes or T wave variations. Seven individuals had normal tracings. The standard exercise test was well performed by twenty-nine, fairly well by six, poorly by five and badly by one.

Attempts to plot correlation curves between the four diagnostic criteria (murmur grade, size of heart, ECG changes and exercise test) were more successful here than in the group of patients with mitral insufficiency. In general it was found that the candidates with grade 4 murmurs had larger hearts, more electrocardiographic changes and a poorer exercise tolerance than in the other murmur grades; beyond this generalization there was considerable individual variation. One man with a grade 1 presystolic murmur, for example, had the largest heart in the entire group, a good exercise test and no ECG changes; another had a grade 3 murmur, a small heart, a fair exercise test and considerable ECG abnormality (P-R interval delayed to 0.28 second, QRS of 0.14 second, with slurring and right axis deviation). Still another had a grade 2 murmur, slightly enlarged heart, normal ECG and a poor exercise test. One

gained the impression, however, that as a group mitral stenosis in its asymptomatic stage is productive of more objective cardiac disorders than mitral insufficiency.

Aortic Insufficiency was discovered in 22 of the 169 valvular cases or about 13 per cent. Grading of the diastolic murmurs seemed to present more difficulty to the examiners than any other type of murmur and there were many honest differences of opinion in regard to the following distribution of the murmur grade classification:* seven candidates had a grade 1 diastolic murmur, four had grade 2, eight had grade 3 and three had grade 4. As to heart size eleven had normal measurements, six had a slight increase in size, three a moderate increase and two had marked enlargement of the cardiac x-ray. The electrocardiographic studies showed twelve with normal tracings, six with simple left axis deviation and five with miscellaneous defects in addition to left axis deviation. The exercise tolerance test was well performed by sixteen, fairly well by two and poorly by four.

The correlation curves here showed only two significant findings: First, increase in heart size was accompanied by left axis deviation of various degrees not necessarily to the same extent. The largest heart had a moderate left axis deviation compared to a moderately enlarged heart which had a maximum left axis deviation. The second finding was a close coincidence between heart size and exercise tolerance; the larger the heart the poorer the effort response. There was an interesting relationship between the grade of the murmur and the three other diagnostic criteria plotted as a single curve; increase in the grading of these three factors also multiplied their unit value. Thus, a grade 1 diastolic murmur might be unassociated with any other finding while a grade 2 murmur might have either some enlargement of the heart and ECG abnormality or a decreased exercise tolerance. A grade 3 murmur might have a combination of any two of those first mentioned and grade 4 would probably have all three. It was the correlation trend in this curve which made the proper evaluation of the murmur grading so important in the original examination and this explains why so much attention was devoted to the qualities of the diastolic murmur.

Aortic Stenosis. Only nine cases of aortic valvular stenosis were discovered; these represent but 6 per cent of the valvular lesions found and only 2.5 per cent of the total number of cardiac individuals in the asymptomatic group. The number seems small compared to the general incidence of aortic stenosis and the other valvular diseases seen in the cardiac clinic; perhaps aortic stenosis is less asymptomatic and more productive of subjective complaints than other lesions.

A breakdown of the figures shows that of the nine patients three were classified as grade 1 systolic murmurs, two as grade 2, two as grade 3 and two as grade 4. X-ray mensuration showed five to be of normal size, one slightly increased, three moderately increased and none markedly increased. The electrocardiograms revealed seven normal tracings, one left axis deviation and one intraventricular block with a QRS of 0.16 second. The exercise tolerance results indicated six with good response, one with fair response, two with poor response and none with bad response.

This group was too small to develop any significant trends in the correlation curves but there was a suggestion that some relation existed between heart size and exercise tolerance; the three moderately enlarged hearts all had less than normal effort response.

Congenital Heart Disease. Four candidates were diagnosed with congenital lesions

* Many of these patients were studied by simultaneous electrocardiographic, polygraphic and heart sound recordings made at the naval hospital. The timing of the murmur rarely caused any difficulty but the qualities of pitch, intensity and duration cannot be determined from phonocardiographic tracings made by the conventional apparatus. The special equipment used at the Adler Heart Sound Laboratory to produce phonograph records of heart sounds and murmurs for teaching purposes does, however, show these qualities and many of the candidates received a special work-up through the courtesy of the Louis Adler Cardiovascular Research Fund.

because of the character, timing and quality of the murmurs which were discovered. Two patients had continuous low pitched rumbling murmurs heard throughout the cardiac cycle with maximum intensity over the upper end of the sternum; one patient appeared to have a septal defect and the other a possible aneurysm of the pulmonic artery with an open ductus arteriosus. These patients form the subject of a paper to be published later.[1]

A review of all these patients with valvular disorders shows that correlation curves obtained by plotting (1) type, quality and intensity of the murmur expressed in terms of grading from 1 to 4; (2) x-ray mensuration of the heart; (3) electrocardiographic and (4) functional response to exercise can be obtained in certain forms of asymptomatic valvular heart disease. Both mitral stenosis and aortic insufficiency show one or more such curves; aortic stenosis has a tendency to follow a coincident curve between heart size and exercise tolerance. No curves could be obtained in the study of mitral insufficiency although these individuals formed the largest group with valvular heart lesions.

HYPERTENSION

There were eighty-nine candidates for enlistment who had high blood pressure without symptoms or previous knowledge of the condition. The group divided into subclasses consisting of 10 mm. differences in systolic blood pressure is presented in Table III. The diastolic levels presented no problems and they are not considered here.

There are many clinical examinations and laboratory tests which can be made in the study of hypertension; only seven were selected for expediency and for economy of time, material and labor. These were: (1) clinical appraisal of the heart—rate, rhythm and murmurs; (2) x-ray mensuration; (3) electrocardiographic study; (4) exercise tolerance; (5) examination of the retinal arteries; (6) urinalysis and (7) other obvious pathologic conditions.

While the patients were classified into the various groups given in Table III in order to show distribution of the systolic levels in 10 mm. differences, it was found that no significant trends in the correlation curves were obtained in the 10 mm. subdivisions so that this study was made by considering groups with 20 mm. differences. Thus, the first two groups with pressures from 150 to 170 are considered together, the third and fourth groups with pressures from 170 to 190 and the fifth and sixth groups with pressures from 190 to 210 are combined. The single individual with a pressure from 210 to 220 will be considered alone.

TABLE III
DISTRIBUTION OF THE SYSTOLIC BLOOD PRESSURE LEVELS IN THE HYPERTENSIVE ASYMPTOMATIC GROUP

	Cases
150 to 160 mm. Hg	31
160 to 170	27
170 to 180	18
180 to 190	7
190 to 200	2
200 to 210	3
210 to 220	1
Total	89

There were fifty-eight candidates referred for examination who had systolic blood pressure levels from 150 to 170. Only three of them were found to have cardiac disturbances (two had systolic murmurs and one had tachycardia). Five had enlargement of the heart; seven had ECG changes (delayed P-R interval in two, left axis deviation in four and wide QRS in one). Exercise tolerance was poorly performed in three. Funduscopy showed five with retinal artery changes. Urinalysis was abnormal in one (albumin present). Four had other conditions (one migraine, 1 gallbladder disease, one possible pulmonary tuberculosis by x-ray findings and one early hyperthyroidism).

In considering this group no correlation curves could be determined in plotting the seven diagnostic criteria against the various pressure levels or against each other. The group was, however, large enough to make certain generalizations: First, systolic blood pressure levels up to 170 have a minimum of objective pathologic disturbances and

secondly, no relation exists between the early types of disturbances as they tend to develop.

In the next group with pressures from 170 to 190 there were twenty-five candidates. Five had definite cardiac disturbances (two with gallop rhythm, two with systolic murmurs and one with tachycardia). Eleven had enlargement of the heart; nine had ECG changes (delayed P-R interval in three, five with left axis deviation and one with a bundle branch disorder). Sixteen had poor exercise tolerance tests; ten had retinal artery changes; five had abnormal urinalysis; four had other conditions (diabetes, one; possible gastric ulcer, one and chronic arthritis, two). Eleven individuals had no discoverable disorders.

The correlation curves in this group showed several significant trends: (1) a drop in the exercise tolerance tests occurred most commonly; (2) enlargement of the heart is the next most common finding; (3) changes in the retinal arteries come next in frequency; (4) ECG changes occurred in less then one-third of the patients; (5) cardiac disturbances and renal damage were found in only one-fifth of the group; (6) enlargement of the heart and ECG changes follow a coincident curve; (7) all of the patients with renal damage had retinal artery changes; (8) a poor exercise test may occur independently of any other finding but every patient with objective evidence of pathologic disorders had a poor effort response.

In the third group with pressures from 190 to 210 there were only five patients. Of these two had cardiac disturbances (gallop rhythm) and four had enlargement of the heart. All five had ECG changes (left axis deviation and one with T_1 iso-electric). Exercise tolerance was poorly performed in all patients; four had retinal artery changes, one very severe. Two had urinary evidence of renal damage and one had another condition (chronic pancreatitis).

This series is too small to draw anything but the general impression that systolic blood pressures in these higher levels is associated with considerable objective pathologic conditions measured in the terms of the seven diagnostic criteria employed in the examination.

The single individual with a pressure in the 210 to 220 group had gallop rhythm, some enlargement of the heart, slight left axis deviation, fair exercise test, moderate hypertensive retinopathy and no other condition except a marked psychosomatic background which, however, did not lead to any symptoms referable to the hypertension.

In reviewing the data of the entire asymptomatic hypertensive group a few interesting observations may be made: Perhaps the most important is the fact that high levels of blood pressure may develop without subjective symptoms of any kind; this stands in contrast to the host of embellished complaints suffered by many patients with hypertension. Headaches, dizzy spells, "black outs," giddiness, nausea, vomiting, weakness, tremulousness, numbness and visual disturbances are but a few of the symptoms which cause such patients to seek medical attention. Every one of these patients denied symptoms of any kind, past or present.

The second observation is that objective pathologic conditions as the result of or associated with high blood pressure start to develop in significant trends when systolic levels rise above 170. Most of the patients with pressures below 170 had no cardiovascular changes while most of those with pressures above 170 had one or more abnormalities. In this series 170 seems to have been the critical dividing point of the two groups and this figure is of considerable interest in relation to the findings in psychosomatic hypertension.[2]

IRREGULARITIES OF THE HEART

Disturbances of cardiac rhythm were discovered in fifty-five patients; these were classified as shown in Table IV.

Extrasystoles. Electrocardiographic studies of these twenty-seven individuals showed the ectopic focus for the premature beats to have been in the ventricles in

eighteen patients, in the auricles in six, in the junctional area in two and one had a bifocal (auricle and ventricle) extrasystolic pattern. Considered in terms of frequency four had one or less premature beats per minute, eleven had from two to

TABLE IV

ASYMPTOMATIC IRREGULARITIES OF THE HEART

Extrasystoles	27
Tachycardia (over 110)	19
Auricular fibrillation	6
Heart block (complete)	2
Heart block (incomplete)	1
Total	55

three, five had from three to four, two had from four to five, three had from five to six and two had more than six extrasystoles per minute. The group as a whole was singularly free from cardiovascular disease. Only one of the twenty-seven had an enlarged heart and two had apical systolic murmurs. All had good exercise tolerance curves; all had normal blood pressures and there was no evidence of any other abnormal condition.

All of these individuals were symptom-free; this is interesting since the most common cause of heart consciousness and palpitation which occurs without effort is premature contractions. Strictly speaking, it is not the extrasystole which is responsible for the sensation or the awareness of the disturbance in the rhythm of the heart but the sinus beat following the ectopic one. Since the extrasystole is premature, it causes contraction of the left ventricle before it is completely filled; if it occurs very early in diastole, there may be insufficient blood in the ventricle to open the aortic valves. The refractory period which follows the premature contraction is usually much longer than the normal diastolic filling period, and the next sinus beat is thus accompanied by a greater volume output, sometimes as much as 80 per cent greater. This pulsation is transmitted throughout the entire arterial tree and subjective symptoms will arise in any tissue or organ which may be neuroreceptor-sensitive to increased systolic pressure and blood volume changes.

Such hemodynamic disturbances are not confined to the extrasystolic arrhythmias; they may also occur in auricular fibrillation and in incomplete heart block. The condition may be and usually is productive of many subjective complaints. Since all of these patients were asymptomatic, they were more carefully studied by graphic registration of the electrocardiogram and simultaneous polygrams of the radial pulse. Of the twenty-seven all but three had the effective type of premature contraction, i. e., the ectopic beat occurred late enough in diastole to permit the aortic valves to open and the extrasystole was transmitted through the arterial system as a small premature beat. This type of premature contraction is ordinarily not perceived by the patient since the hemodynamic disturbance is minimal.

The other three candidates had ineffective premature contractions, i. e., the ectopic beat is so premature that there was insufficient blood present in the left ventricle to open the valves and no pulsation was transmitted to the arteries. In spite of the pressure changes and volume output of the next normal beat none of the three were aware of the disturbance even after it had been pointed out to them. It is these three who are interesting in the discussion of asymptomatic heart disease and they will be considered later in relation to the psychosomatic phenomena of cardiovascular disturbances.

Tachycardia. Nineteen candidates had persistent pulse rates of 110 or over. Three were found to have increased basal metabolic rates (plus 22 to 35 per cent) and one had an x-ray of the lung which was suggestive of reactivated tuberculosis. The remaining fifteen had no discoverable extracardiac cause for the rapid heart action. All were of the parasympathetic habitus described by Wolffe; they also might be considered in the Oppenheimer classification of neurocirculatory asthenia. A better concept suggested by Dreifuss is

based upon the psychosomatic evaluation of the whole condition which is now loosely labeled "cardiac neurosis" or "effort syndrome." This problem has been previously discussed[3] as one of the major subdivisions of psychosomatic heart disease. After more than five years of experience with these patients in relation to the military service it was the author's opinion that they were unfit for combat duty and the entire group of nineteen was disqualified for enlistment.

Auricular Fibrillation. Six candidates had grossly irregular pulses; all proved to be auricular fibrillation by electrocardiographic examination. Five were slow fibrillators with apical rates averaging from 54 to 76 per minute; these had no pulse deficit and were more or less well compensated. On physical examination no murmurs were heard, the hearts were not enlarged and the blood pressures were within normal limits. The exercise tolerance test was fairly well performed by all. None had a history of rheumatic fever and all denied previous cardiac disability.

Like extrasystolic arrhythmia auricular fibrillation may be productive of a variety of subjective complaints and symptoms; these are due to the irregular blood flow, volume changes and pressure alterations. All these factors become exaggerated after exercise since the pacemaker mechanism no longer controls the rate of ventricular contraction. At rest most slow fibrillators have no circulatory deficiency but when the demand for greater volume output occurs, various degrees of decompensation develop. When the so-called idiopathic ventricular rates are within the normal frequency range, work may sometimes be performed with little loss of functional capacity and one is often astonished at the magnitude of the physical tasks performed by such patients without symptoms of any kind.

When the ventricular rates are rapid and over 100 per minute a pulse deficit occurs. The pulse deficit in auricular fibrillation presents the same hemodynamic phenomenon as the premature contractions do in the extrasystolic arrhythmias. Contraction of the empty or poorly filled left ventricle is not accompanied by a pulsation in the arterial tree; the heart contracts but no radial pulse is felt. As the ventricular rate rises in auricular fibrillation the pulse deficit increases and in the rapid rates seen in delirium cordis the ventricular contractions may rise to 180 or 200 with a radial rate of 90 or less. The pulse deficit in some of these patients may be as much as 100 per minute.

Experiments have shown that under such circumstances the per minute volume of blood delivered by the left ventricle to the arterial system may be reduced to 85 per cent of normal and congestive failure rapidly develops. Between the well compensated non-deficit type of auricular fibrillation and the stage just described is a large ill defined group of patients who carry on moderate activity with a minimum of subjective discomfort.

One of the six candidates with auricular fibrillation was one of this group. He had a ventricular rate of 108 and a radial rate of 88; the deficit here was 20. He had a slightly enlarged heart and a grade 3 systolic murmur could be heard over the mitral area. The ECG showed a left axis deviation in addition to fibrillation. The blood pressure was 118/66. The exercise test was fairly well performed and he had no signs of confestive failure although the venous pressure appeared to be increased. This patient was twenty-four years old and had been working for more than two years as a helper on a parcel delivery service, a job which required considerable labor and long hours. He was intelligent and alert but was completely unaware of any cardiac disability; the author had seen similar cases previously.

Asymptomatic auricular fibrillation is most likely to occur in those patients who do not have a history of rheumatic fever or valvular heart disease, particularly mitral stenosis; it is seen most frequently in patients with spontaneous or idiopathic auricular fibrillation and the condition may only be discovered by chance unless one or more of the intravascular complications of

the condition occurs (embolization, infarction or cerebral accidents).

All of the six candidates for enlistment were rejected as the disturbance, even though it may be asymptomatic, is sooner or later a serious cardiac disability. The prognosis in any given case is quite unpredictable; certain individuals have been known to pursue perfectly normal lives for many years. Other individuals may break down abruptly for no obvious reason. As a group they are poor military risks even for limited duty.

Heart Block. (Complete auricular and ventricular dissociation). Two candidates were discovered to have complete heart block, one with a ventricular rate of 44 and the other 60 per minute. The first case was suspected at the original recruiting examination because of the low pulse rate; the patient said he always had a slow pulse and he remembered as a child being told that his heart was not beating as fast as normal but he denied symptoms of any kind and had followed his work as an accountant without difficulty. He had been examined at the age of twenty-three and passed for life insurance; his present age was twenty-five.

On examination the heart sounds were of good tonal quality; no murmurs were heard. X-ray showed no change in heart size. His blood pressure was 140/88. ECG showed a regular auricular rate of 74 and a ventricular rate of 44. There was no axis deviation but the QRS was spread to 0.12 second. The precordial leads CF_3, CF_4 and CF_5 showed a T wave inversion. The exercise test was fairly well performed as far as dyspnea was concerned but no change occurred in the radial rate.

The evidence here suggested a congenital type of A-V dissociation; ordinarily there is a compensatory hypertrophy of the left ventricle to meet the demand for a greater volume output than that which can be delivered at the slow rate of 44. In certain cases of juvenile complete block, enlargement of the heart with corresponding left axis deviation may develop rather late. In this patient a satisfactory adjustment had apparently been made in his hemodynamic balance and no secondary changes had as yet appeared.

The second man was more interesting. He was sent to the cardiac clinic for study because his heart rate did not speed up after the exercise test; from this single finding a presumptive diagnosis of complete heart block was made notwithstanding the "normal" pulse rate of 60. He was thirty-one years old, a chemistry teacher, more or less active in athletics, with a negative history except for two attacks of tonsillitis, an appendectomy and a fractured humerus as a child. He denied previous cardiac disability of any kind and had passed successfully several physical examinations for insurance and civil service. The heart was not increased in size by x-ray. The heart sounds were of good tonal quality and regular. No murmurs were heard. Blood pressure was 134/90 and ECG showed an auricular rate of 78 and a ventricular rate of 60; the QRS was at the upper limit of normal (0.10 second) but there was no other abnormality either in the limb or precordial leads. The exercise test was fairly well performed except for slight dyspnea and no change in the pulse rate.

With the diagnosis established, a closer examination revealed other signs of A-V dissociation: asynchronous pulsations in the carotid arteries and jugular veins, absent vagal respiratory changes in the pulse rate and changes in the first heart sound from beat to beat. Complete heart block with idioventricular rates in the 60's and 70's are not as uncommon as the earlier writers have reported. From 1925 to 1934 the author was fond of demonstrating to his students the case of a man with a pulse rate of 72 who had complete A-V dissociation with considerable myocardial damage; he worked as an elevator operator in the hospital for nearly twelve years with a minimum of cardiac disability; he has reported other such cases with high idioventricular rates.[4]

As indicated previously many patients with complete heart block are usually free

from symptoms while at rest; it is only when ventricular output fails to meet circulatory demands that signs of failure develop. Dyspnea and heart pain occur first; pulmonary congestion and peripheral edema occur later. When idioventricular rates become very slow, from 30 to 20 per minute, cerebral anoxemia is the predominating symptom with episodes of fainting and unconsciousness; this was described nearly a century ago by Stokes and later by Adams. With the higher ventricular rates, from 56 to 76, many patients may, however, be free from symptoms even after considerable exercise but sooner or later the inadequate output from the heart will make itself felt. Such individuals, of course, make poor military material and must be rejected even though their present cardiovascular status appears competent.

Incomplete heart block with an occasional missed ventricular beat was found in one candidate. He was referred for cardiac investigation with a diagnosis of extrasystolic arrhythmia. Without ECG study the two conditions cannot be distinguished; the compensatory pause following the premature contraction is recognized by the examiner and sometimes the patient as a "skipped beat." A ventricular beat which is blocked at the A-V node appears also as a missing or dropped beat between two normal beats. Whereas extrasystoles are not ordinarily disqualifying for enlistment, incomplete heart block represents a type of cardiac disease which is sufficient to reject a candidate.

This man was a thirty-three year old carpenter who was anxious to get into a Seabee unit. He denied a rheumatic history and had no previous cardiac disability; he had been working at his trade for about fifteen years without a single day's union sick benefits. On physical examination the heart was somewhat increased in size by X-ray. The heart sounds were of fair tonal quality, regular, 76 with four to six skipped beats per minute. These skipped beats were not increased by exercise and they persisted after a period of bed rest. A soft systolic murmur, grade 2, was heard at the apex but this was considered functional since it had many postural changes and disappeared after exercise. The ECG showed a P-R internal prolonged to 0.26 second, the QRS was normal but there was slight left axis deviation. ST and T were normal. The precordial lead CF_4 was normal. Every twelfth to fifteenth P wave was not followed by a QRS complex; there was no Wenckebach effect.

The candidate was not conscious of the skipped beat and the exercise test was well performed. This type of incomplete heart block with a 12:11 rhythm usually does not remain in this pattern; either the ratio increases to the more familiar 4:3, 3:2 or 2:1 rates or the phenomenon of the blocked beat entirely disappears, leaving the patient with a prolonged P-R interval or so-called first degree heart block. This man was seen three times over a period of eight weeks with no change in the general electrocardiographic pattern. In spite of all of the examinations which he had gone through and even though he had been the focus of considerable medical attention, he was still asymptomatic and could not identify the skipped beats when they occurred. He represents the minimum in psychosomatic reaction.

In summary, of the eighty-five candidates referred for irregularities of the heart only the group of twenty-seven with premature contractions were accepted. The others all had cardiac disturbances which were disqualifying although entirely asymptomatic. Of special interest here was the group of fibrillators and their general freedom from cardiovascular complaints even after the effort tolerance tests.

CARDIAC HYPERTROPHY

Simple enlargement of the heart was found in twenty-six candidates; the diagnosis was chiefly made by x-ray mensuration. A routine recruiting chest film was made upon each applicant for enlistment in both the Navy and Marine Corps; this

was done largely to screen out tuberculosis suspects. From time to time other conditions were discovered in the chest films and these patients received additional x-ray examinations. Twenty-one of the candidates were picked out this way and referred to the cardiac clinic for further study. The remaining five were discovered by the examining physicians at the enlistment offices; all of these patients either had an apex impulse outside of the mid-clavicular line, or below the fifth interspace or both.

On detailed examination none of the group had murmurs of any kind. The ECG study showed seven with left axis deviation, one with early right axis deviation, two with prolonged P-R intervals (0.22 and 0.26 second), one with an intraventricular block pattern (QRS delayed to 0.14 second) and the remaining fifteen were within normal limits. The blood pressure was normal in twenty-three; the other three were 148/90, 150/88 and 154/94. The exercise tolerance test was well performed by eighteen, fairly well performed by three, poorly performed by three and badly performed by one.

No correlation curves could be drawn from the size of the heart, ECG findings, blood pressure or exercise tolerance curves. The only significant trend was in relation to heart size and left axis deviation; the seven patients with left axis deviation came within those having the ten largest hearts. The hypertensive patients only had moderately enlarged hearts but one had the intraventricular block pattern.

These candidates were closely questioned in regard to their participation in past or present athletics. There was a history of more than moderate athletic activity in fifteen of the twenty-six, moderate activity in seven and four said that they had not been interested in physical sports; in other words, twenty-two of the twenty-six had engaged in athletics in one degree or another. In view of the current discussion in regard to the so-called athletic heart this figure may perhaps be of some significance since it is the single most common factor found in the group with cardiac hypertrophy.

Cardiac hypertrophy of unknown origin has received the attention of many authors[5] but in the cases reported nearly all of the patients have had severe symptoms. Levy and Von Glahn have recently published a series of ten fatal cases[6] but there are other reports of individuals with "idiopathic" cardiac hypertrophy who have lived for a considerable period of time after discovery of the condition. The available literature says nothing, however, about the outlook of such patients who are without subjective symptoms of any kind.

In considering the eligibility of this group for military service many problems were discussed by the medical officers charged with forming a policy to be followed in such candidates. When simple enlargement of the heart existed without any other finding, i. e., electrocardiographic changes, hypertension, lowered exercise tolerance or other cardiac disability, the individual was accepted. Of the twenty-six only four, which was less than 15 per cent, were qualified for enlistment.

ARTERIOSCLEROSIS

Premature arterial changes were discovered in eleven candidates; this was about 3 per cent of the entire asymptomatic cardiovascular group. The diagnosis of premature arteriosclerosis was made when the degree of vascular change was inconsistent with the age period. The age distribution showed one candidate twenty-seven years old, one aged thirty, two aged thirty-four, one aged thirty-six, four aged thirty-eight, one aged forty and one aged forty-two.

The peripheral vascular examination was standardized for economy of time and labor; the following tests were recorded upon all patients of the vascular group who were referred for study: (1) palpation of the radials, posterior tibials, dorsalis pedis, temporals and any other available artery to determine rigidity, mineralization and other abnormalities; (2) blood pressure of the brachials, femorals and dorsalis pedis; (3) oscillometric readings of both arms and

legs; (4) x-ray visualization when mineralization was present or suspected; (5) funduscopy; (6) thermal changes of the feet; (7) color changes of the feet; (8) special x-ray films of the aorta and (9) when indicated, electrocardiographic studies.

A review of this data showed that the most common finding was increased rigidity and thickening of the radial arteries; this occurred in nine of the eleven patients. Tortuosity and thickening of the temporal arteries were found in six, retinal vascular changes in five, oscillometric abnormalities were discovered in the legs of three, thermal and color changes in two and x-ray visualization of the tibials was found in one. No significant trends could be determined from the correlation curves; the series was perhaps too small to show possible relationships. These patients required more laboratory investigation than was considered necessary for the enlistment examination; blood chemistry data in regard to cholesterol, N. P. N., sugar, chlorides, calcium and renal function tests would have made the study more valuable.

The three candidates with oscillometric changes in the vessels of the legs presented some interesting findings: Two had complete obliteration of the dorsalis pedis pulsations in both feet, both had color and thermal changes. One was a man of thirty-eight, the other was forty-two. Both denied peripheral vascular symptoms of any kind and it was only the dusky cyanosis of their feet which called attention to need for further study at the original enlistment examination. These patients stand in sharp contrast to the usual symptoms and complaints given by most individuals with vascular disturbances of the extremities; minor degrees of vascular change may be accompanied by considerable pain and disability. When the condition becomes as advanced as that shown by these two men, there is ordinarily a history of many years of pain and suffering. Asymptomatic peripheral vascular disease is sometimes picked up accidentally in the course of a general physical examination, but the experience in most cardiovascular clinics is that the syndrome is not a silent one and most patients have subjective symptoms far out of proportion to the actual degree of circulatory impairment found.

While the youth of some of the candidates with vascular disease is perhaps unexpected, the actual number of individuals with premature arterial changes who were discovered was extremely small. The eleven selected are presented here because they were without symptoms or previous medical history; about forty-five other candidates with arterial conditions and with symptoms were also seen. Thus, a total of only fifty-six individuals of the many thousands who were examined for enlistment were found to have early vascular disease. These statistics are interesting in relation to the alleged increase in the number of young people with arterial diseases.

COMMENT

In considering these 350 individuals with cardiovascular disorders and without symptoms several interesting questions arise for which there are, perhaps, no acceptable answers. Indeed, some of the fundamental problems involved are not primarily cardiovascular at all but common to the entire pain receptor mechanism of the patient. Why were these candidates without pain and symptoms? With the heart admitted to be a specially sensitive organ why, for example, were 169 with valvular heart disease and fifty-five with irregularities of the pulse free from subjective complaints of any kind? With peripheral vascular disease as a painful and disabling condition, why did two of these patients with advanced arterial disturbances of the feet not have a single complaint? Again, hypertension is productive of many subjective symptoms but eighty-nine candidates with high blood pressure were symptom-free. Why? In short, what explanation can be given for the asymptomatic course of these various cardiovascular conditions and what is responsible for the lack of subjective response?

Less than a decade ago it would have been considered pure speculation to have attempted any explanation concerning the variability of sensory response to visceral stimulation, but some of the concepts of psychosomatic medicine have done much to clarify many of these confusing clinical phenomena. The heart as an organ entity (Wolffe) is peculiarly responsive to psychomotor stimuli and like the gastrointestinal and central nervous systems it may initiate somatic symptoms in a degree far out of proportion to the primary receptor mechanism stimulus. At the same time primary somatic stimuli arising within the heart itself as the result of a disturbed or pathologic physiology find a track into consciousness by way of the same or similar receptor system pathways. When the factors conditioning the common pathways are used frequently enough or when a pseudo-reflex develops in linking the autonomic and central nervous system via a sensitized tissue or organ, the subjective symptoms which develop are equally appreciated in consciousness regardless of whether the stimulus actually arose in the heart itself or whether the entire syndrome is extracardiac.

On the other hand, these pathways to consciousness may be poorly developed or physiologically blocked in certain individuals. There are a number of possible variants which can explain this phenomenon: (1) tissue injury does not produce a somatic stimulus; (2) the stimulus if produced is reduced on its way to consciousness; (3) a psychomotor stimulus from the same or different tissue using the same pathway modifies the somatic stimulus either by reduction or amplification; (4) the psychomotor stimulus may receive priority in consciousness; (5) any combination of the aforementioned may occur.

In addition to these factors which are chiefly related to the visceral organs without direct afferent sensory connections to the brain must be considered the individual's idiopathic threshold to painful stimuli (Libman). There is a paradoxical relationship between a patient's psychosomatic response and his relative threshold to pain; in brief, while it is true that nearly all psychosomatics have low thresholds in the response to painful stimuli, not all persons with low thresholds are psychosomatic personalities.

Only relatively few of the candidates with asymptomatic heart disease were tested for pain threshold; time and circumstance did not permit the study that these patients merited but a group of sixty were selected at random during the course of the seven month-period covered by this report. They represent a fair sample of the various cardiovascular conditions already described. Of the sixty, fourteen had a low threshold for pain, forty-four were considered within the normal range of sensitivity and two had a high threshold. The fourteen with the low thresholds should have been symptomatic according to Reisman's theory but they were not. What combination of factors is responsible for this? Perhaps the answer will come from the vast research projects in psychosomatic phenomena now being stimulated as a result of the war.

In closing, let us now turn to a consideration of the more factual data of this report. A group of 350 individuals with various types of cardiovascular disease have been presented, none of whom had the usual or expected symptoms and complaints of patients suffering from these conditions. An opportunity was presented to study heart and blood vessel disorders from a purely objective point of view; the examiner was uninfluenced by what the patient said and the final opinion and diagnosis in each case was the result of physical findings alone. In evaluating these data certain correlation curves were attempted between various diagnostic criteria in order to present a more complete and accurate clinical picture of some common cardiovascular disorders.

Results in certain respects are confirmatory of impressions previously gained from cardiac clinic experience; statistically a number of generally held opinions are found to be true. When the series in individual conditions has been large enough,

significant trends have indicated important relationships in the development of cardiac syndromes. Taken together these data should prove to be helpful in diagnosis and evaluation of disabilities arising from heart and blood vessel disease.

SUMMARY

1. A group of 350 men within the age periods of seventeen to fifty-one discovered to have cardiovascular disease on examination for enlistment in the Navy and Marine Corps were studied because they were free from subjective symptoms of any kind. The opportunity for investigating asymptomatic heart disease has previously been limited to isolated cases. Since subjective complaints play such a great rôle in nearly every cardiac patient, this study is an attempt to evaluate the factual data in different forms of cardiovascular disturbances free from the usual psychosomatic background.

2. These men were classified into five general groups for purposes of comparative studies: (1) valvular heart disease; (2) hypertension; (3) cardiac irregularities; (4) simple cardiac hypertrophy; (5) premature vascular disease.

3. In valvular heart disease certain correlation curves could be obtained between heart size, type of murmur, electrocardiographic changes and exercise tolerance tests.

4. In the hypertensive group correlation curves were attempted between the clinical appraisal of the heart itself, x-ray mensuration, ECG, exercise tolerance test, funduscopy, urinalysis and other associated tests.

5. Cardiac irregularities included the extrasystolic arrhythmias, tachycardia, auricular fibrillation, incomplete heart block and complete A-V dissociation. Only the group with premature contractions were accepted for enlistment.

6. Simple cardiac hypertrophy showed certain correlation curves which disqualified most of the candidates; only four of twenty-six were accepted.

7. The candidates with various types of peripheral vascular disease and other arterial disturbances were also disqualified although they were asymptomatic.

8. A possible explanation concerning the freedom from subjective symptoms and complaints in this group of 350 individuals is presented; the theory of development of psychosomatic phenomena in cardiovascular disease and its relation to the pain receptor mechanisms of the autonomic system are discussed.

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Significance of Electrocardiographic Changes in Rheumatic Fever*

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CARDITIS is one of the major criteria by which rheumatic fever can be recognized. In determining the presence of carditis in any given case abnormalities in the electrocardiogram are often the sole objective findings of cardiac involvement. In the young adults who came under our observation at the Naval Hospital in Oakland, California and who were made the basis of this study, unequivocal evidence of carditis, such as cardiac enlargement, significant diastolic murmurs, acute pericarditis or congestive failure were not commonly observed during attacks of rheumatic fever. Subjective symptoms such as dyspnea and precordial pain are suggestive but not sufficiently clean cut for diagnosis. Systolic murmurs, because of their frequency in any febrile disease associated with tachycardia as well as in normal individuals, are difficult to evaluate. Systolic murmurs that appear while the patient is under observation for possible rheumatic fever, or are long, loud and varying but little with position or respiration are of more definite diagnostic value. Muffled heart sounds of poor quality are frequently heard but are difficult to evaluate. The changing quality of the heart sounds with improvement of the patient is often suggestive of cardiac involvement. The electrocardiogram must be relied upon to a large extent to determine the presence of carditis. This is true not only in the initial diagnosis but also to determine the presence of continued rheumatic activity or recrudescence. The necessity for exercising the greatest care in evaluating minor electrocardiographic abnormalities must be re-emphasized, especially in view of the recent studies in service personnel[1,2] that demonstrate the widened range of variants in normal individuals. The changes in the electrocardiogram to be described are not specific solely for rheumatic fever, but when present in this disease indicate involvement of the heart.

Based on several hundred cases of rheumatic fever personally observed the following points will be discussed: types of electrocardiographic abnormalities seen, diagnostic value of these abnormalities in unusual or subacute rheumatic fever, duration of the abnormalities, value of repeated electrocardiograms in assessing continued rheumatic activity or recrudescence (often present without other clinical or laboratory signs), absence or insignificance of electrocardiographic abnormalities in the presence of carditis and fixed residual electrocardiographic changes which are occasionally seen. Various types of abnormalities will be illustrated by case reports.

Partial Heart Block in Rheumatic Fever. It is well known that the most common abnormality noted in the electrocardiogram in rheumatic fever is a partial A-V heart block.[3–15] The experience gained from our material confirms this opinion as 60 per cent of the abnormalities found were conduction defects. (Table 1.) The determination of the frequency of delayed A-V conduction in any series depends, in part, on

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the criteria demanded for this diagnosis. Ashman and Hull[16] have noted the reciprocal relationship of the cardiac rate and the normal P-R interval and have indicated that in the presence of tachycardia the upper limits of normal A-V conduction may be less

TABLE I

ECG ABNORMALITIES IN RHEUMATIC FEVER

Total cases of rheumatic fever		700
Total cases with abnormalities in the ECG		147 (21%)
Of the 147 cases:		
1. Conduction defects		88 (60%)
Partial A-V block	83	
Complete A-V block	3	
Intraventricular block	2	
2. T wave changes		52 (35%)
Inversion $T_{1,2}$ or $_4$	17	
Diphasic T_1 and T_4	11	
Flat T_1 and T_4	24	
3. Abnormal rhythms		14 (10%)
Shifting auricular pacemaker	7	
Nodal rhythm	4	
Nodal escape	2	
Auricular fibrillation	1	
4. Miscellaneous		12 (8%)
Marked LAD or RAD	7	
Inversion P_2 and P_3	5	

TABLE II

DURATION OF A-V BLOCK IN RHEUMATIC FEVER

Of 76 cases: Days	No.	Per Cent
0– 4	11	(15)
5– 8	3	(4)
9–14	39	(51)
15–21	14	(18)
22–28	6	(8)
over 3 months	3	(4)

than 0.20 second. They have also shown that in children the upper limits of normal A-V conduction are usually less than 0.20 second. These statements, however, have not received universal acceptance and no patient in our series was considered to have a prolonged P-R interval unless it exceeded 0.20 second. It is apparent that had the P-R interval been related to the cardiac rate in our series the percentage of patients with abnormal conduction would have been higher because of the frequent occurrence of tachycardia at the onset of rheumatic fever. In borderline records with P-R intervals of 0.20 to 0.22 second a reduction of at least 0.04 second in a clinically improved patient was considered as indicative of a partial A-V block. Table II shows that 4 per cent of the patients who had delayed A-V conduction during the acute phases of rheumatic fever had apparently fixed conduction defects. The P-R interval remained prolonged for months after all signs of rheumatic activity had subsided even though the patient was allowed to get up and to be fully active. This fact must be considered before interpreting an isolated, prolonged P-R found in a routine electrocardiogram as indicative of acute carditis. The occasional observation of a prolonged P-R interval in normal aviators[1,2] may be explained at times on the basis of rheumatic fever from a previous episode.

The transient nature of the abnormalities in conduction has been noted in the literature. The conflicting percentages of abnormal electrocardiograms in rheumatic fever can probably be attributed to the stage of the disease at which the tracings were made and the frequency with which they were taken in serial records. The extremely short duration of the abnormalities noted in some of our patients was quite striking from hours to a few days. (Fig. 1.) Data on the average duration of the delayed A-V conduction are summarized in Table II and cases illustrating the transient nature of the abnormalities follow:

CASE REPORTS

CASE I. B. N. S., aged seventeen, was admitted to the hospital on April 4, 1944, with a history of minimal swelling and pain in the feet of three days' duration. The pain in the feet had progressed to such a degree of severity within forty-eight hours that he had been unable to sleep. Physical examination gave negative results except for a red throat and a temperature of 101°F. It was elicited, however, that he had had a cold and a sore throat intermittently since January, 1944, and four years previously he had had a febrile polyarthritis diagnosed as rheumatic fever.

The patient was placed in bed and 10 Gm. of salicylates daily were administered. He became afebrile and asymptomatic within forty-eight hours. An electrocardiogram on April 5th revealed a partial A-V block with a P-R of 0.28 second. A tracing taken a week later was

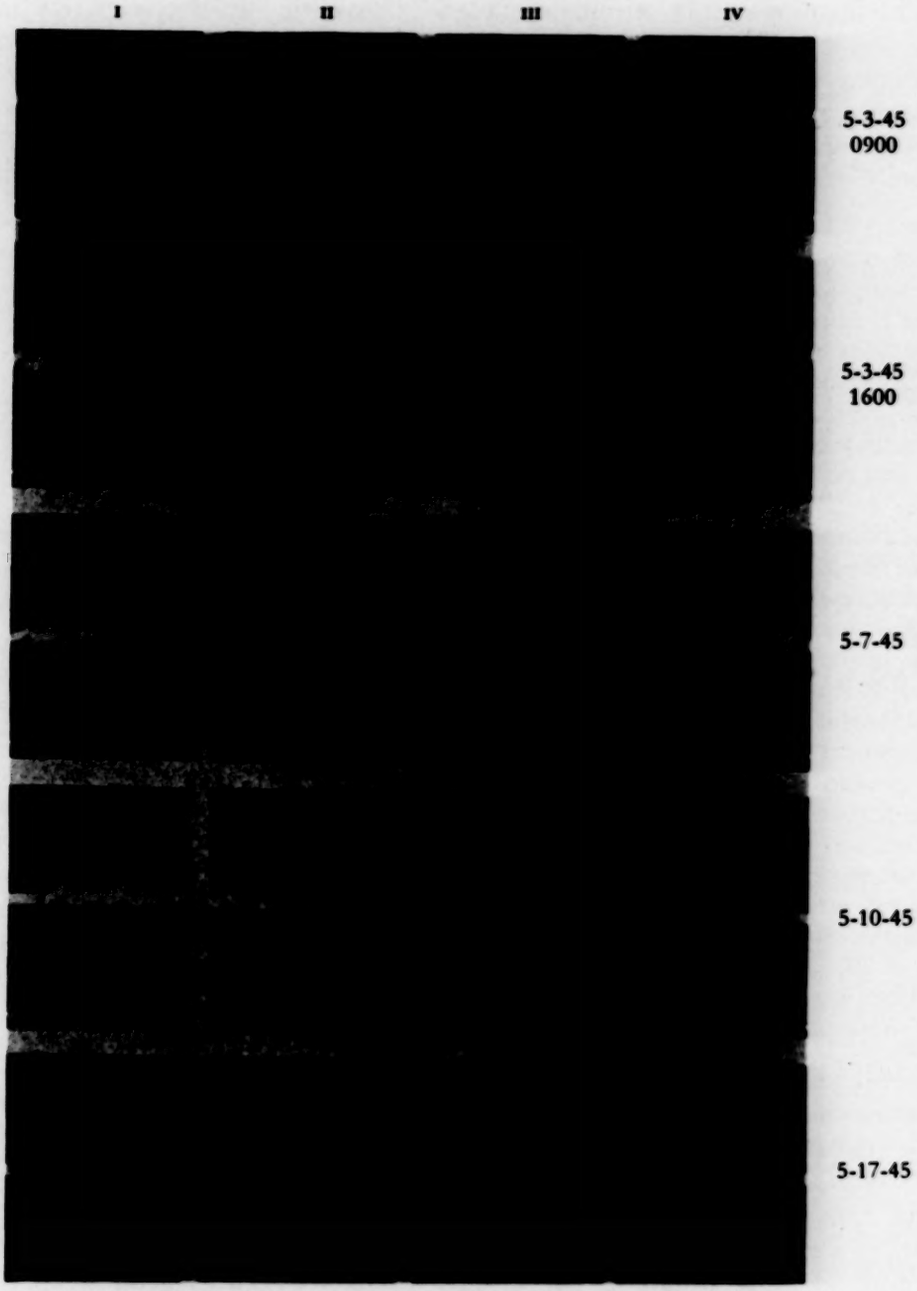

FIG. 1. Patient W. C. J., white, age nineteen. Onset of rheumatic fever occurred on February 23, 1945. Temperatures on May 3, 7, 10 and 17, 1945, were 99.2°, 98.8°, 98.6° and 99.4°F., respectively. Electrocardiogram indicates precordial pain on May 3rd as 0900 and 1600.

normal, with a P-R of 0.18 second. Clinically, the heart showed no sign of abnormality. The sedimentation rate (Westergren, the method used throughout our studies) had been 25 mm. in one hour on entry, but on serial readings gradually fell as follows: 21, 16, 15, 14, 11, 12, 10, 14, 9, to reach 6 mm. in one hour on June 12th, about two months after admission.

Comment: The electrocardiogram in this case furnished the only evidence of carditis in a patient who had no objective signs of arthritis and who complained only of pain in the feet which rapidly subsided. The initial fever had been attributed to residual pharyngitis by the admitting officer. The

electrocardiogram led to a more detailed history which revealed the previous attack of rheumatic fever. The partial A-V block was present for only one week although two months elapsed before the lowest sedimentation rate was reached.

CASE II. T. R. H., aged eighteen, was admitted to the hospital on June 11, 1943. He had recently arrived in San Francisco from an endemic rheumatic fever area in the Northwest. He complained of stiffness of his knees, ankles and elbows and stated that he had first noted the symptoms a week before. Further history revealed frequent episodes of sore throat and a weight loss of 20 pounds during his period of training as a recruit a few months before. Physical examination, including the heart, gave negative results and he was afebrile. The sedimentation rate, however, was 28 mm. in one hour and an electrocardiogram revealed a variable heart block, from partial to complete, with a P-R from 0.24 to 0.40 second. At times a nodal rhythm was present. Roentgenographic examination of the thorax gave negative results.

The patient was put to bed and salicylates were administered. By June 15, 1943, four days later, he was practically asymptomatic. No abnormal signs had appeared in the heart. The electrocardiogram was normal at this point and remained so. Serial sedimentation rates revealed figures of 28, 31, 15, 11 and on July 21st, five weeks later, it was 8 mm. in one hour.

Comment: Case II illustrates the value of the electrocardiogram as a diagnostic procedure in young adults with vague arthralgias. Rheumatic fever was suspected in this patient because he came from a highly endemic area and because he had had many episodes of soreness of the throat. Although his symptoms were minimal, the electrocardiogram indicated the presence of myocarditis. The short duration of the partial A-V block, four days only, is noteworthy.

T Wave Changes in Rheumatic Fever. Emphasis in the literature has always been placed on partial A-V block as the characteristic electrocardiographic abnormality in rheumatic fever. As stated our experience confirms this fact and the cases already reported stress the transient nature of the abnormality. We have been impressed, however, by the relatively high incidence of T wave abnormalities in the absence of clinical pericarditis, 35 per cent of our abnormal electrocardiograms in rheumatic fever being in this category. The T wave abnormalities occur often without associated defects in A-V conduction, but it is not uncommon to have both delayed A-V conduction and abnormal T waves in the same tracing. Significant abnormalities of the S-T segment were infrequently seen although at times a slight elevation of this segment was observed in the limb leads which did not exceed that found normally. The appearance of T wave changes in rheumatic fever has been noted in the literature[12–14,17–19] but their frequency and importance as isolated findings has not been sufficiently emphasized. The types and duration of the T wave abnormalities are illustrated in Tables I and III. The inverted T waves in rheumatic fever may be short-lived, may be intermittent and variable similar to the features noted in A-V conduction and may involve Leads I, II or IV, alone or in combination. (Figs. 2 to 4.) Depending on the time the electrocardiogram is taken, changes may be seen solely in one lead (Fig. 2, 5/11) whereas at an earlier or later date other leads may be abnormal. (Fig. 2, 5/10 and 5/19.) Special care must be used to see that the precordial electrode is placed over the cardiac apex before interpreting the electrocardiogram as abnormal on the basis solely of an inverted T_4. Multiple precordial leads should be taken if doubt exists as to the position of the apical electrode. At times T_1 may be low and borderline, (Fig. 3, 4/30) but serial changes subsequently may reveal T_1

TABLE III

DURATION OF T WAVE CHANGES IN RHEUMATIC FEVER

Acute pericarditis excluded; flat T waves excluded; duration noted until T_1, T_2, T_4 upright 1 mm.

Of 28 cases:

Days	
0– 4	4
5– 8	11
9–14	9
15–28	2
over 28	2

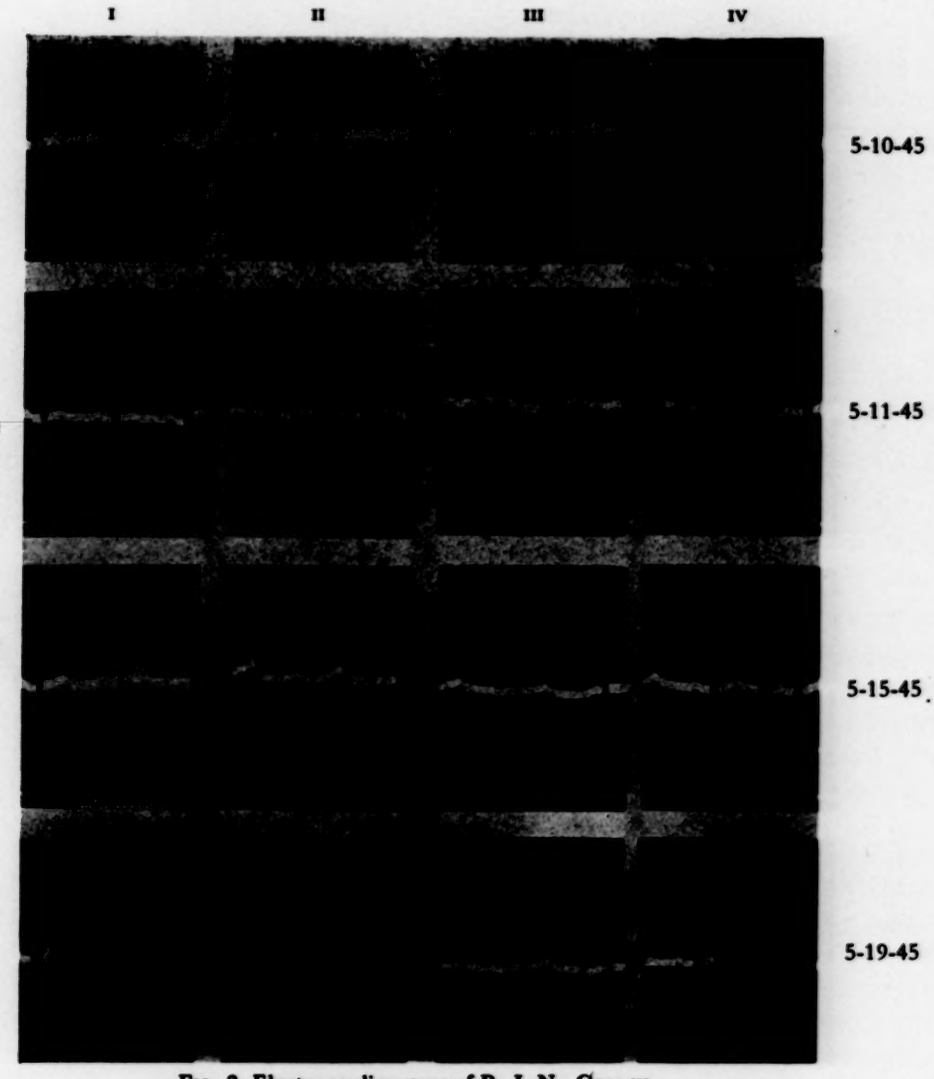

FIG. 2. Electrocardiograms of R. J. N., Case III.

to be taller (5/17), indicating that the low T_1 seen earlier was significant. These considerations emphasize the importance of serial electrocardiograms in rheumatic fever. If the patient whose records are shown in Figure 2 had had a single tracing on 5/15, the record would have been interpreted as normal yet on 5/11 and 5/19 the electrocardiogram clearly showed abnormal findings.

CASE III. R. J. N., aged twenty-eight, had been placed on the sick list on his ship on April 4, 1945, complaining of painful, swollen joints of a week's duration. His knees were involved first and over a three-day period his symptoms progressed from soreness and pain on motion to swelling and inability to walk. On the day before he reported to the sick bay migratory polyarthritis of the ankles, elbows, wrists and feet appeared. He had had no previous rheumatic episodes but had had a sore throat ten days prior to onset of his articular symptoms. Examination on April 4th revealed swollen, red, painful metacarpophalangeal joints, and tenderness and stiffness of the elbows and knees without swelling. The heart was normal. The temperature was 101.4°F., pulse 96 and blood pressure 124/78. The erythrocyte count was 4,100,000 and the leukocyte count 17,850 per cu. mm. of blood. The sedimentation rate was 28 mm. in one hour. The electrocardiogram at that time revealed a normal P-R interval but there was inversion of T_1 and T_2 with a flat T_3. Roentgenographic examination of the thorax gave negative results. The patient had no precordial

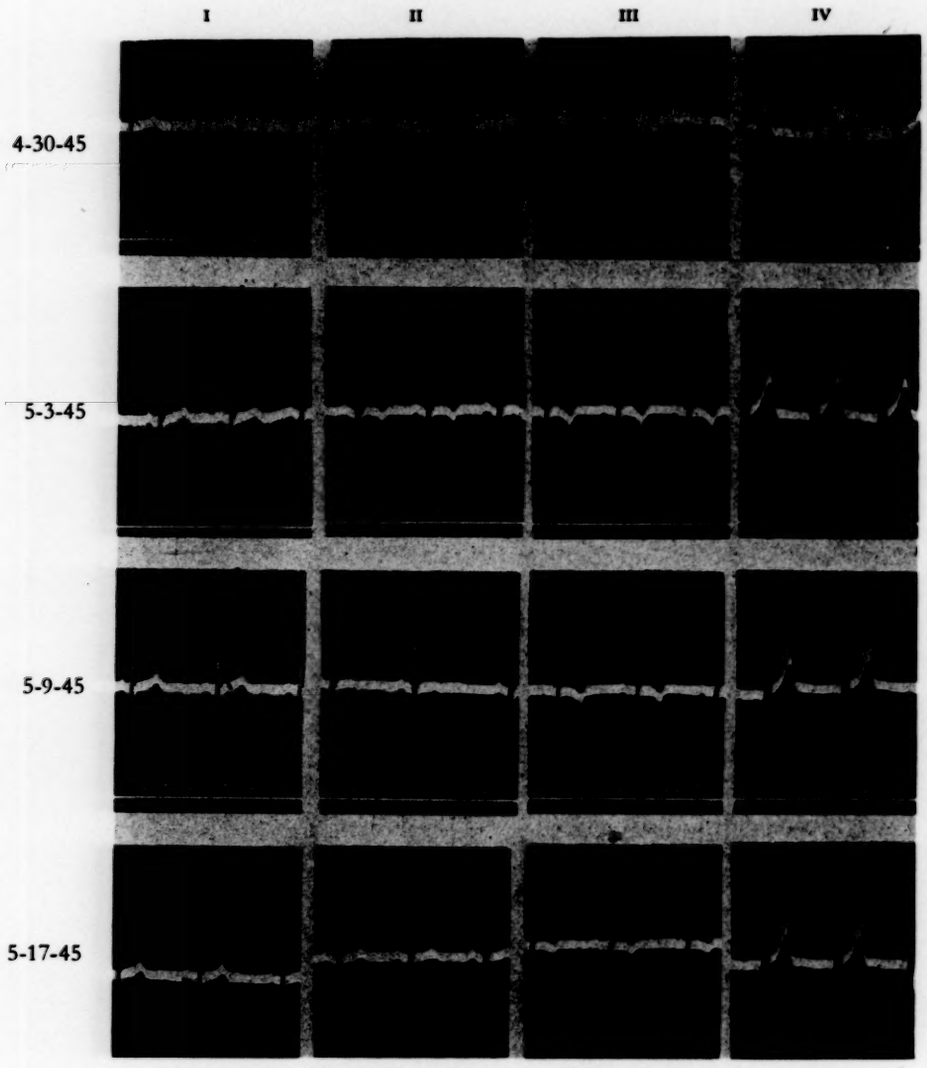

FIG. 3. Electrocardiograms of R. J. N., Case III.

pain, dyspnea or cough and the heart was normal on repeated physical examinations.

On arrival at the hospital on April 25, 1945, the patient made no complaints and physical examination showed no abnormalities. In view of his history he was put on routine rheumatic fever care. The leukocyte count at this time was 10,000 per cu. mm. of blood and the sedimentation rate 23 mm. in one hour. The electrocardiogram revealed a low T_1, inverted T_2 and T_3 and a normal upright T_4. The A-V conduction was normal. Serial electrocardiographic tracings were made and the changes in the T waves are seen in Figure 3. On May 3rd, T_1 was slightly taller but T_2 remained inverted. By May 9th, T_2 was low diphasic and T_1 and T_4 were normal. On May 11th, T_2 was normally upright and the sedimentation rate had fallen to 8 mm. in one hour.

Comment: Case III illustrates a type of T wave abnormality commonly seen. T_2 is often the last to become normal. In this patient one month elapsed before the electrocardiogram was normal. At no time were there precordial pain, signs or symptoms of pericarditis and the heart was not enlarged. Partial heart block did not occur.

CASE IV. J. M. G., aged seventeen, while on a troop train en route to San Francisco, awoke with a painful right elbow without swelling or redness. On the following day the elbow was improved but the patient had pain in the lower region of his back. Four days after the initial attack he noted swelling and redness of the left ankle and the next day his right ankle became red and swollen and the left knee was painful although not swollen. He had felt perfectly well

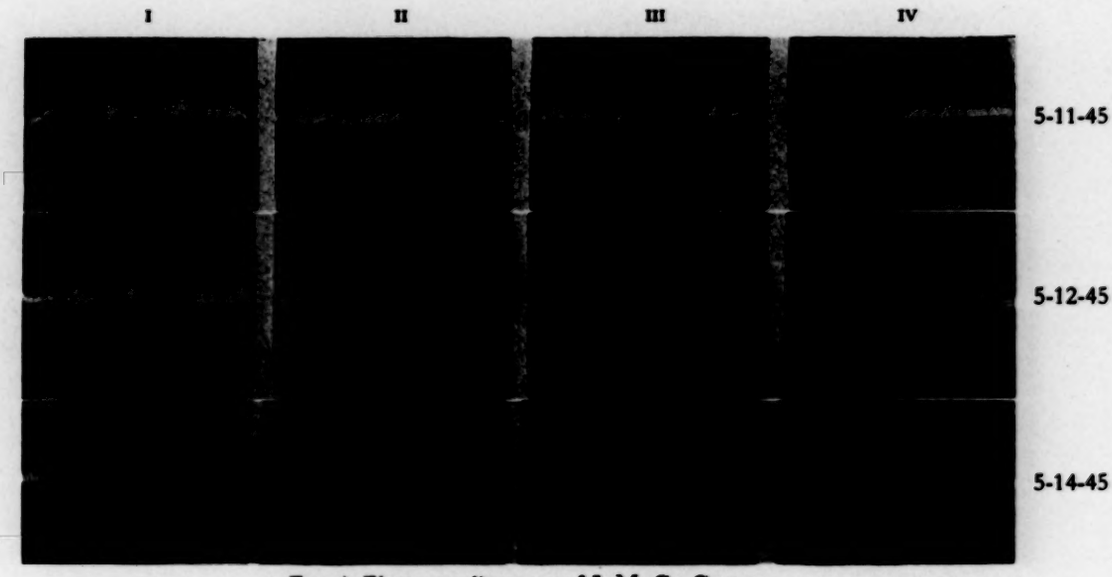

FIG. 4. Electrocardiograms of J. M. G., Case IV.

prior to this episode and had had no previous rheumatic history and no upper respiratory infection had preceded the present episode.

On arrival at the hospital on May 11th, he complained of dyspnea and fatigue on walking, pain and swelling in both ankles and pain in the left knee. A physical examination confirmed the presence of arthritis, with redness, swelling, tenderness and pain on motion of the ankles. The temperature was 100°F. The heart was not enlarged, but there was a grade 2 apical blowing systolic murmur. The urine was normal and the blood Kahn reaction was negative. There was no anemia. The leukocyte count was 12,000 per cu. mm. of blood and the sedimentation rate was 23 mm. in one hour. The electrocardiogram revealed an inverted T_4.

The patient was put to bed and given the usual dose of 10 Gm. of sodium salicylate daily. The joints improved with striking rapidity and there were neither subjective nor objective manifestations of arthritis within forty-eight to seventy-two hours. He was afebrile in thirty-six hours. The sedimentation rate fell rapidly, being 23 mm. on May 14th and 16 and 7 mm. in one hour on May 21st. The electrocardiogram showed a sequential change in T_4. This T wave became diphasic in twenty-four and normally upright in forty-eight hours. (Fig. 4.)

Comment: Case IV shows that abnormalities in T_4 may be the only deviation from normal in the electrocardiographic tracing and that these changes may be transient, just as was shown for the partial heart block. This patient had complete symptomatic, febrile and electrocardiographic subsidence to normal within forty-eight to seventy-two hours of hospitalization. The sedimentation rate became normal in ten days. The entire episode was the shortest observed in a definitive attack of rheumatic fever.

Miscellaneous Abnormalities in Rheumatic Fever. Table I shows that abnormalities not associated with conduction defects or T wave changes were present in 18 per cent of patients with abnormal electrocardiograms. Such changes, however, rarely are present as isolated findings and when occurring alone are not considered indicative of carditis although they direct attention to the heart. When the electrocardiographic changes parallel clinical rheumatic activity and disappear with clinical recovery, one probably is justified in assuming that they represent active myocarditis. Extrasystoles were occasionally noted in our patients but were not included in the table because of the frequency with which transient premature beats occur normally. Ectopic beats with relatively rapid cardiac rates have on occasion suggested the possibility of rheumatic fever, especially when they occur in young individuals in the weeks following an infection due to hemolytic streptococcus. Master and Jaffe[20] found premature contractions of the heart in

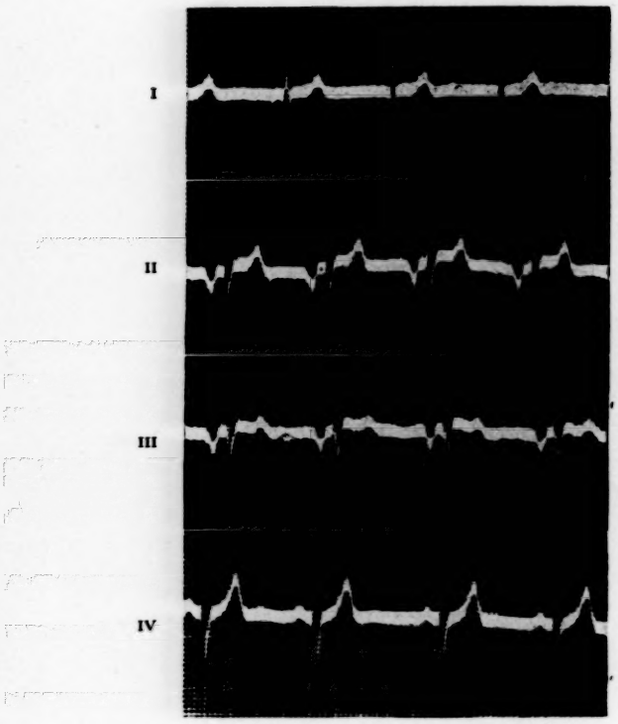

FIG. 5. Electrocardiograms of R. C. A., age twenty-one, who had rheumatic fever.

15 per cent of sixty-three patients with rheumatic fever. These authors observed auricular fibrillation in 3.2 per cent of their patients. This is in contrast to the rarity with which this arrhythmia was found in our patients and in the series of Parkinson et al.[8] The P wave changes[28] (Fig. 5) may be associated with the auricular lesions described by MacCollum.[21] Filberbaum et al.[15] have also noted that significant P wave abnormalities, especially when serial changes occur, appear to be definite evidence of rheumatic cardiac involvement.

Residual Electrocardiographic Changes as Only Sign of Rheumatic Activity. Occasionally abnormalities in the electrocardiogram persist as the only signs of rheumatic activity after all other signs and symptoms have disappeared and the sedimentation rate has become normal. The question then arises as to whether such abnormalities are fixed and irreversible or whether myocarditis persists and appropriate treatment is still required. If the patient is seen for the first time at this stage with an abnormal electrocardiogram, the problem of interpretation becomes even more difficult. It has been our experience that irreversible delayed A-V conduction persists in approximately 4 per cent of patients with rheumatic fever who had a partial A-V block during the acute phase while persistence of T wave abnormalities is less common. Nevertheless, when a patient with rheumatic fever is kept under observation in whom the electrocardiographic abnormalities have not disappeared, the residual abnormalities should be considered as indicative of rheumatic activity until proved otherwise. The patients whose cases are to be reported in the following were placed on continued rest in bed for a reasonable period after the subsidence of all signs of activity except those of an abnormal electrocardiogram. These patients were then allowed to get up cautiously and both had evidences of mild recrudescence, indicating that even though the electrocardiographic abnormalities were isolated signs of activity they were significant. In other cases, however, recrudescence did not occur even after full physical activity was allowed; electrocardiographic abnormalities persisted as the sole objective vestige of the previous rheumatic fever.

CASE V. S. G. M., aged twenty-two, was admitted to the hospital on March 6, 1945. He had had a previous attack of rheumatic fever in 1939, lasting one month. His present episode began on February 13, 1945, without antecedent upper respiratory or other infection of which he was aware. A migratory polyarthritis of the left knee, shoulders, left wrist and hands developed, the joints being involved in succession a few days apart and each becoming improved in three to four days. On February 26th, he noticed dyspnea on walking and there was some aching abdominal pain with mild diarrhea. He reported to his local sick bay at which examination revealed a temperature of 101.6°F., pulse of 116 and respiration of 24. His blood pressure was 125/75. The heart was not enlarged but there was a long, blowing apical systolic murmur, grade 2, and the pulmonary second sound was greatly accentuated. No rub was audible. The involved joints were swollen, painful on motion and tender. The laboratory data revealed no anemia, a leukocyte count of 10,000

with 76 per cent polymorphonuclear cells. The sedimentation rate was 25 mm. in one hour. The electrocardiogram showed a P-R interval of 0.20 second, delayed for the tachycardia. T_1 and T_2 were low and T_4 was diphasic.

The patient was put to bed and given 30 gr. of sodium salicylate every four hours; he complained of severe tinnitus and deafness after twelve hours so the dose was reduced to 20 gr. every four hours which alleviated the toxic symptoms. He showed marked clinical improvement in seventy-two hours as far as fever and articular symptoms were concerned, but on March 3rd, a soft, early aortic diastolic murmur was heard.

On arrival at the hospital on March 6th, the patient had moderate tenderness in his knees, shoulders, elbows and left wrist but he complained only of mild aching in the joints. His temperature was 99°F., pulse 84 and respiration 20. Cardiac findings were unchanged. Urine was negative but the hemoglobin was 71 per cent and the prothrombin 75 per cent. The sedimentation rate was 19 mm. in one hour. The electrocardiogram showed a P-R of 0.24 second; T_1, T_2 and T_4 were inverted. He was placed on rest in bed and salicylates and within seventy-two hours the aching in the joints had subsided. He remained afebrile. The aortic diastolic murmur disappeared and the apical systolic murmur decreased in intensity. The sedimentation rate gradually fell to a normal level of 10 mm. in one hour on April 11, and 5 mm. in one hour by April 17, 1945, forty-two days after entry. The P-R interval had increased to 0.40 second on March 14th, was 0.33 second on March 19th, and again on March 22nd, but by April 6th, it was 0.20 second with a cardiac rate of 73. The T waves were still abnormal on this date but had changed from inverted to low diphasic in leads I and IV. By April 23rd, he was afebrile, asymptomatic and the sedimentation rate had been normal for two weeks. The P-R interval was 0.20 second but T_1 was still flat and T_4 slightly inverted. The patient was anxious to get up and the question arose as to the significance of the residual T changes since they were the only signs of activity. It was decided to allow him to get up and about the ward for an hour, twice daily, and to observe the results. Within a week T_1, T_2 and T_4 had again become inverted; after two weeks the P-R interval had increased to 0.40 second. He had no symptoms or rise in temperature despite the increase in electrocardiographic abnormalities. The sedimentation rate increased from 3 mm. in one hour on April 23rd, to 13 mm. in one hour on May 10, 1945. He was returned to complete rest in bed and by May 20th, the T waves were low to flat. The patient was then transferred to a convalescent hospital.

Comment: Case V illustrates that residual T wave abnormalities, even though not marked, may represent the only objective evidence of continued rheumatic activity. Interpretation is facilitated when a single physician follows the course of the disease, but it may be very difficult if the patient is seen at a late stage without the benefit of previous electrocardiographic studies. If this patient had first been observed on April 23, 1945, the significance of the flat T waves would have been difficult to evaluate. Careful observation when a patient is first allowed to get up will aid in evaluating the significance of residual electrocardiographic abnormalities. This case emphasizes the importance of the advice of Barnes[22] that a patient should be kept in bed until all signs of activity have disappeared; residual electrocardiographic changes as isolated findings must be considered as such signs. Only continued observation will allow one to conclude that residual electrocardiographic changes are fixed and not necessarily associated with rheumatic activity.

CASE VI. G. A. Z., aged thirty-one, was admitted to the hospital on December 3, 1944. He had been overseas for twenty-two months when in mid-October of 1944 migratory polyarthritis developed and he complained of fever, fatigue and hiccups. He was treated with rest in bed and salicylates. One month before his transfer he began to have palpitations and for three days prior to entry he had continued to ache in the region of his precordium. Administration of salicylates had been discontinued for one month.

On arrival he complained of aching in the precordium, palpitations, fatigue and aching pain in the wrists, knees and ankles. Examination gave negative results except for slight pain on full range of motion of the affected joints. The temperature was 99.6°F., pulse 105 and

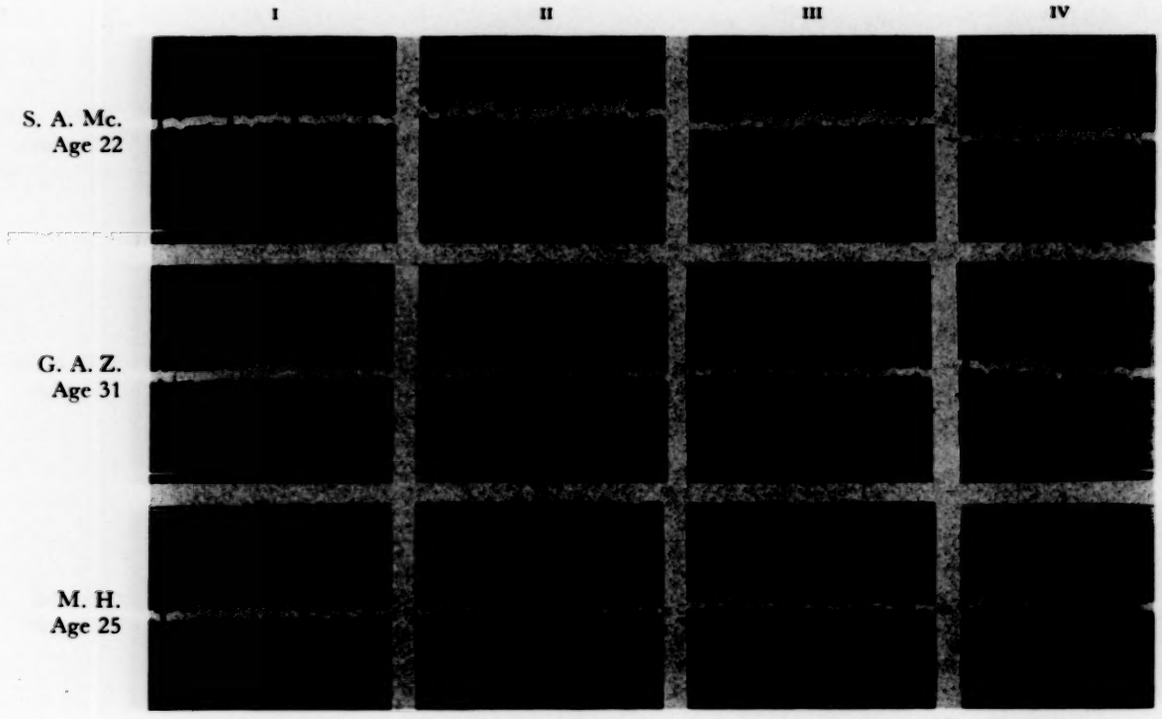

FIG. 6. Electrocardiograms showing T changes in rheumatic fever in three patients.

respiration 20. Laboratory data revealed a normal urine, normal hemoglobin and erythrocyte count, a leukocyte count of 10,000, sedimentation rate of 7 mm. in one hour and a negative blood Kahn reaction. Roentgenologic examination of the thorax was negative; the heart was not enlarged. The electrocardiogram showed the P-R to be delayed, being 0.21 second with a cardiac rate of 101. T_1 and T_4 were inverted, T_2 was flat. (Fig. 6.)

The patient was put to bed and given full doses of salicylates. The sedimentation rates were normal on repeated tests, he was afebrile within three days and by January 9, 1945, he had no pain in the joint or the precordium. By January 15th, the P-R was normal, being 0.19 second, with a cardiac rate of 75 while T_1 was flat to low upright and T_4 small and slightly inverted. He was then transferred to a convalescent hospital.

Comment: Case VI illustrates again that abnormalities in the electrocardiogram may be the major objective evidences of residual rheumatic activity. In this patient salicylate therapy had been discontinued; he complained of fatigue, palpitations, painful joints and aching in the precordial region and had a temperature of 99.6°F. for three days. The sedimentation rate was normal when checked twice a week during the six weeks of observation. The electrocardiogram revealed abnormal T waves and delayed A-V conduction. The symptoms and low fever subsided with salicylate therapy, the A-V conduction became normal but six weeks later the T waves had not yet become normal. Although active carditis was present in this patient as well as the one discussed in Case V, the sedimentation rate was normal at the time in each instance. This is of special interest since, as a general rule, the sedimentation rate is the last sign to become normal.

Negative Electrocardiograms in the Presence of Clinical Myocarditis and Endocarditis. It is important to indicate limitations of the electrocardiogram and to emphasize the fact that this test does not replace, but is an adjunct to, careful clinical study. In some patients with rheumatic fever definite carditis as manifested by cardiac enlargement or significant diastolic murmurs may appear without diagnostic electrocardiographic changes. Repeated examination of the heart is therefore essential in managing a

patient with rheumatic fever to determine the presence of carditis. This is particularly true since diastolic murmurs may not be present at the onset of rheumatic fever and may not appear for several weeks after the acute febrile and articular manifestations have subsided (Case v) and the patient apparently is progressing satisfactorily.

CASE VII. J. F. E., aged twenty-five, was admitted to the hospital on April 3, 1945, with a diagnosis of acute arthritis. He had had a sore throat on several occasions in the past two years, the last time on February 15, 1945. On March 10th, he had an aching pain in the right knee but without swelling. He continued ambulant but a week later the pain was so severe he could not stand and swelling had appeared in the knee. He reported to his sick bay at which time it was noted that his right knee was swollen, red, hot and tender. The sedimentation rate was 25 mm. in one hour and the temperature 100.2°F. The patient was put to bed with hot packs and given 3 Gm. of salicylates daily. He was afebrile in five days and the symptoms present in the knee subsided in a week. The sedimentation rate was 10 mm. in one hour on March 26th. No electrocardiogram was taken. The patient was returned to duty on March 29th. Within forty-eight hours, pain and swelling in the right knee had reappeared and the left knee was similarly affected the next day. The patient was then transferred to us.

On arrival he had a temperature of 100°F. and slight swelling and tenderness of both knees. The heart was normal. Laboratory data revealed moderate anemia. The sedimentation rate was 25 mm. in one hour and the electrocardiogram was normal.

The patient was placed on salicylates, 10 Gm. daily, and put to bed. He was afebrile within twenty-four hours and the joints were normal within a week. Serial electrocardiograms, taken twice weekly for two months, remained normal. The sedimentation rate fell gradually, serial determinations twice a week being 18, 15, 13, 11, 12, 10, 14, 13 and finally 5 mm. in one hour on May 21st, seven weeks after entry.

On May 22nd when the sedimentation rate was 5 mm. in one hour and the patient was afebrile, subcutaneous nodules about the knees were noted. On full range of motion the knees were slightly painful. The patient was still on salicylates. He felt "washed out" and was easily fatigued upon the slightest exertion. At this period an early aortic diastolic murmur was noted which persisted until the patient was transferred to a convalescent hospital. The sedimentation rate remained normal to the last, being 5 and 6 mm. in one hour on subsequent determinations.

Comment: Case VII illustrates: (1) initial monarticular involvement, (2) rapidity of recurrence with premature physical activity, (3) the need for clinical as well as electrocardiographic study since serial tracings were normal and yet a diastolic murmur appeared and (4) the presence of rheumatic activity despite a normal sedimentation rate. The diagnosis of rheumatic fever was not made during the initial attack of arthritis in this patient, presumably because of the rapid response to rest and small doses of salicylates.

CASE VIII. F. W. T., aged twenty-six, became ill with scarlet fever on February 21, 1945. He recovered promptly and was apparently well until March 17th, when he complained of aching pain in the ankles and feet of four days' duration which became so severe that he could not stand or walk. In the succeeding ten days his fingers, wrists, knees and shoulders became involved and he was transferred to the hospital on March 27, 1945. Examination revealed a temperature of 100.4°F., slightly enlarged tonsils, subcutaneous nodules over the tendons of the fingertips and an erythematous rash over the flexor surface of the right arm. The ankles and soles were tender and swollen and the skin over the feet showed typical postscarlatinal desquamation. The heart was normal; the urine showed a trace of albumin; the sedimentation rate was 26 mm. in one hour. The blood count showed a hemoglobin of 11 Gm.; the leukocyte count was 15,400; the electrocardiogram was normal.

The patient rapidly improved on routine rheumatic fever therapy but continued to complain of fatigue. An electrocardiogram was taken twice weekly and remained negative throughout his course in the hospital. On April 30th, when the patient was afebrile and the joints were normal, a soft, early diastolic murmur was noted. The murmur was consistently present from then on until the patient was transferred to a convalescent hospital on May

8th. The sedimentation rate remained elevated, being 20 mm. in one hour at the time of transfer.

Comment: Cases VII and VIII emphasize the necessity for constant vigilance and searching for significant murmurs even though the electrocardiogram remains normal. It is noteworthy that the aortic diastolic murmur appeared relatively late in the course of the disease when the acute febrile and arthritic phase had subsided.

COMMENTS

It is clear from the cases presented here that the electrocardiogram reveals unequivocal evidence of carditis in some cases of rheumatic fever in which the diagnosis would otherwise be in doubt. Partial heart block and inversion of the T waves in leads other than III are of diagnostic significance when they occur in an illness compatible with rheumatic fever. This is especially true if the improvement in the electrocardiogram parallels the clinical progress of the patient. The appearance of typical electrocardiographic patterns has clarified the nature of many mild cases of illness following streptococcic infections, revealing that they represent changes due to rheumatic fever. The transient nature of the abnormalities makes it necessary to obtain electrocardiographic tracings as early as possible and to repeat them frequently in the course of the disease.

The late appearance of transient abnormalities in the electrocardiogram when the patient seems to be progressing well is valuable in pointing out subclinical recrudescence characteristic of polycyclic rheumatic fever. These changes may occur while the patient is still in bed on salicylate therapy and without the patient being aware of the recrudescent activity.

Control of the process of ambulation during convalescence by use of frequent electrocardiograms is very important. Evidence of reactivation may be first or even solely manifested by the characteristic partial A-V block, inverted T waves, or both and may be entirely subclinical. It is important to recognize this reactivation so as to take the necessary therapeutic measures to minimize damage to the heart.

Diagnosis of rheumatic fever is not warranted when electrocardiographic changes, such as described, appear as isolated findings in a routine electrocardiogram in the absence of symptoms compatible with rheumatic fever. The range of normal variations in the electrocardiogram is great; some patients may have had previous myocarditis and unless the abnormalities disappear in a short time parallel with the clinical symptoms, diagnosis of rheumatic fever cannot be made. Abnormalities in the electrocardiogram which do not disappear with treatment or which may be a normal variant cannot be used as evidence of active carditis, except in those patients with obvious clinical rheumatic fever with carditis in whom the electrocardiographic abnormalities remain fixed and do not revert to normal as the rheumatic activity subsides.

It must be re-emphasized that although the electrocardiogram reveals carditis in young adults with rheumatic fever more than twice as often as all other criteria of carditis combined, some patients will demonstrate clinical evidence of carditis such as diastolic murmurs and cardiac enlargement in the absence of electrocardiographic abnormalities. Therefore, clinical study must be maintained as reliance solely on the electrocardiogram will inevitably lead to errors.

The mechanism of the T wave changes occurring in rheumatic fever is obscure. Symptoms or signs of acute pericarditis are always carefully sought for when inversion of the T wave occurs in all leads even without the preliminary stage of elevated S-T segments. Despite frequent examinations the majority of patients with inverted T waves did not have a pericardial friction rub or enlargement of the cardiac shadow. Subclinical pericarditis cannot be excluded, however, because of the known discrepancy in clinical and autopsy incidence of this finding in rheumatic fever. Bland and Jones[23] found pericarditis present clinically

in 35 per cent of fatal cases of rheumatic fever with some evidence of pericarditis in 80 per cent at autopsy. Electrocardiographic tracings of patients with rheumatic fever without clinical pericarditis are often indistinguishable from tracings of patients with obvious pericarditis. Undoubtedly subclinical pericarditis is responsible for many of the T wave abnormalities previously described.

Involvement of the coronary arteries in rheumatic fever has been frequently noted at autopsy.[24–26] Karsner and Bayless[24] stated that rheumatic fever produces disease of the coronary arteries regularly, with inflammatory or fibrotic lesions. It is possible, therefore, that the T wave changes in rheumatic fever may be the result of coronary arteritis. However, the lack of reciprocal changes in T_1 and T_3 and of S-T and T, so characteristic of arteriosclerotic coronary disease, is against this assumption. Evolutionary changes typical of acute coronary disease,[27] with gradual waxing and waning of the T waves, is almost never seen in rheumatic fever. Anginal pain is rare in rheumatic fever although precordial pain is common, and it is probable that the coronary arteritis of rheumatic fever, as observed on histologic studies, is rarely of clinical significance.

Myocarditis, *per se*, undoubtedly is important in the production of T wave changes and probably shares with subclinical pericarditis the basis of these abnormal electrocardiographic findings. Since subepicardial myocarditis is thought to be responsible for the electrocardiographic changes seen in pericarditis, the common denominator is myocarditis.

SUMMARY

1. The most frequent criterion of carditis in rheumatic fever in young adults is represented by abnormalities in the electrocardiogram. Cardiac enlargement, pericarditis, cardiac failure, diastolic murmurs and unequivocally significant systolic murmurs are relatively infrequent in this group of patients.

2. The most common abnormality in the electrocardiogram in rheumatic fever is a partial A-V block. This is present in 60 per cent of those patients who show electrocardiographic abnormalities.

3. Inversion of T_1, T_2 or T_4, alone or in combination, represents the second most frequent abnormality being found in 35 per cent of those patients in whom electrocardiographic abnormalities are present. Serial records are of value in determining the significance of borderline T changes.

4. Abnormalities in the electrocardiogram other than conduction defects, ST-T wave changes and major arrhythmias occur in rheumatic fever; however, great care must be exercised before interpreting them as indicative of active carditis when they are present as the only abnormal electrocardiographic finding in a single tracing. Significant serial changes may allow one to interpret these minor abnormalities as evidence of cardiac involvement.

5. Significant abnormalities in the electrocardiogram are a major manifestation of rheumatic fever and are of value in recognizing atypical cases.

6. The electrocardiogram may reveal the polycyclic nature of the course of a patient with rheumatic fever in the absence of clinical evidence of such polycyclic activity. This indicates the necessity of taking electrocardiograms early and frequently during the course of the disease.

7. Abnormalities in the electrocardiogram may indicate reactivation of the rheumatic process during convalescence when the patient is first allowed some physical activity. This may occur in association with a secondary rise in fever, elevation of the sedimentation rate or as an isolated finding. The carditis thus revealed may be subclinical and demands appropriate therapy. The process of ambulation requires electrocardiographic observations to determine the presence of renewed activity.

8. Carditis may be obvious clinically in the absence of abnormalities in the electrocardiogram despite early and frequent tracings.

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Oxygen Therapy in Acute Rheumatic Carditis in Children*

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THE physiologic basis for the therapeutic use of oxygen in heart disease lies in the fact that the oxygen tension of the arterial blood may be critically diminished in patients suffering from cardiac disease. Anoxemia of the heart muscle means that the cells of the myocardium receive their supply of oxygen at an abnormally low pressure. The basal consumption of oxygen is not measurably altered. The ill effects are due primarily to the low pressure of free oxygen in the blood to which the cells of the heart muscle are exposed, resulting in a disturbance in cell metabolism. Inhalation of an oxygen-enriched atmosphere containing 40 to 60 per cent oxygen raises the oxygen saturation of the arterial blood to normal in such patients, restoring the oxygen tension and presumably reversing the ill effects of anoxemia. These physiologic principles of oxygen therapy have been adequately summarized by Haldane,[1] Lundsgaard and Van Slyke,[2] Barcroft,[3] Meakins and Davies[4] and Peters and Van Slyke.[5]

Use of oxygen as a therapeutic agent in heart disease has been assiduously explored both in England and in this country for the past twenty-five years. Barach[6] and his associates have studied the effect of oxygen therapy in various types of heart disease and have concluded that in congestive heart failure and in acute coronary thrombosis oxygen very often is a life-saving measure. They were impressed with the fact, however, that successes with this form of therapy were obtained more frequently in the degenerative type of heart disease than in the acute inflammatory type of heart disease such as rheumatic carditis. It is implied from their observations that oxygen therapy is of little value in the treatment of congestive heart failure due to rheumatic heart disease since cardiac failure here is a manifestation of rheumatic activity which may not be altered by oxygen therapy. On the other hand, Poulton[7] has demonstrated that patients suffering from rheumatic carditis with or without failure showed marked clinical improvement when treated in a 50 per cent oxygen atmosphere; there was a rapid fall in temperature and pulse rate, alteration of murmurs, diminution in the size of the heart and significant electrocardiographic changes. He found that the incidence of valvular heart disease was far lower in his treated patients than in the control group of patients. Two years of experience with oxygen therapy in rheumatic carditis in children at the St. Francis Sanatorium confirms the observations of Poulton in the main but also suggests a possible explanation for the failures reported by Barach.

It is the purpose of this paper to present a preliminary report on the effect of oxygen therapy on rheumatic carditis in children. The observations will be limited to a discussion of the effect of long residence in a high oxygen atmosphere upon the clinical course of rheumatic carditis with and without cardiac failure. The mechanisms by which these clinical effects are attained, form the basis for further investigation and will be reported in subsequent papers.

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METHOD OF ADMINISTRATION OF OXYGEN

Methods of administration of oxygen have undergone many changes in the past quarter of a century. These methods are fully described by Barach.[8] The aim has been to develop a method by which adequate and well controlled concentrations of oxygen could be administered to the patient with a minimum of physical and emotional discomfort. Many attempts have been made to build oxygen chambers which would meet these requirements. In England, oxygen chambers were constructed by Barcroft, Hunt and Dufton[9] mainly for physiologic investigation on the deleterious effects of low concentration of oxygen. Similar chambers were used by Campbell and Poulton.[10] In this country, interest was stimulated by the construction of an oxygen chamber at the Rockefeller Institute by Stadie[11] in 1922. At the Mayo Foundation oxygen chambers were constructed in 1926.[12] Barach more recently devised a relatively inexpensive oxygen chamber at the Presbyterian Hospital in New York.[13]

At the Saint Francis Sanatorium two chambers were completed in 1944. These were modeled after the oxygen chamber developed by Barach. By use of pipes containing circulating ice water on one side of the room and a steam radiator on the other (Fig. 1), cooling and drying of the atmosphere, and air movement, is accomplished without the use of noisy motors. Oxygen is delivered from a battery of tanks which are kept in a special room on the laboratory floor. Oxygen pressure in the tanks and the amount of oxygen delivered to each room are carefully controlled. The temperature of the room is kept at a level of 66 to 68°F. by means of rheostats controlling the activity of compressors.

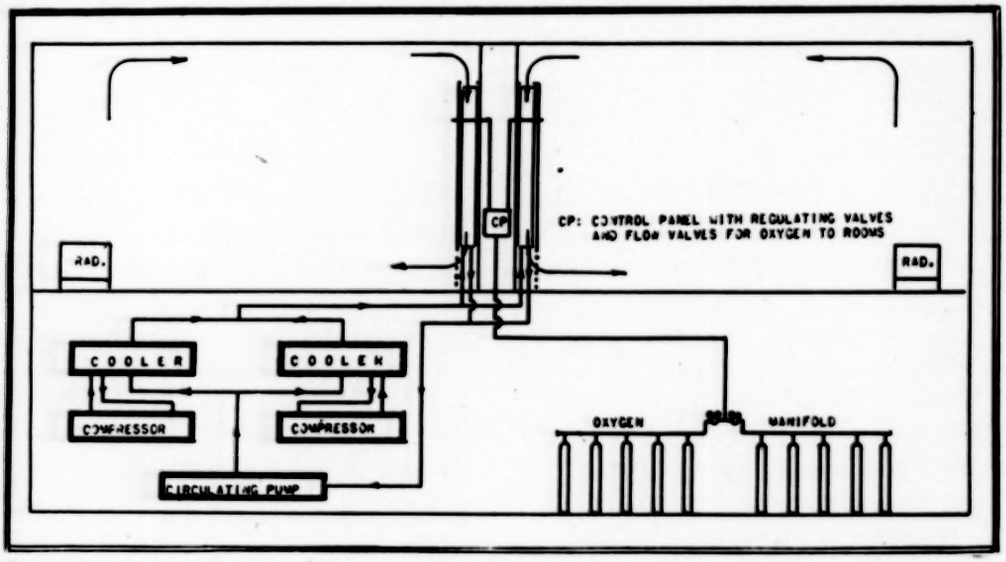

FIG. 1. A schematic diagram of the oxygen chambers showing the air-conditioning unit and also the source of oxygen.

The delivery of oxygen is controlled by flow meters and the concentration of oxygen in the rooms is measured by instruments installed for that purpose. The latter two instruments are within view of the nurse in charge of the rooms. Provisions have been made for sampling of air through a series of tubings leading from the oxygen room to the laboratory floor.

In long-continued oxygen therapy the primary consideration in choosing the method of administration is the comfort of the patient. This is particularly true in the use of oxygen therapy for children. The mask, nasal catheter and tent are poorly tolerated by children. The oxygen room offers many advantages in long-continued oxygen therapy:

1. The oxygen concentration, temperature and humidity of the chambers can be controlled with a high degree of accuracy. Medical and nursing attention can be carried on with practically no variation in the concentration of oxygen. Frequent examination of patients and the carrying on of complex procedures of study and treatment are performed without any change of oxygen concentration of the rooms

and thus with a minimum of discomfort to the patient.

2. All fear implied in oxygen therapy is spared the patient. There is, in most instances, no recognition by the child of the fact that oxygen is being administered. The room does not look unlike any other hospital dormitory. Mechanical appliances and annoying motor noises are absent.

3. The clinical course of cardiac disease in an oxygen-enriched atmosphere can be observed with a minimum of emotional disturbances commonly seen as a result of other methods of oxygen administration.

4. Studies in the physiology of oxygen therapy can be made under highly controlled conditions, and with minimum fluctuations in the desired levels of oxygen concentration, temperature and humidity.

5. Finally, the expense of up-keep is, in our experience, no greater than any other form of oxygen therapy since three children are treated in one room which uses not more than four tanks of oxygen daily. Furthermore, the stability of these rooms and the simplicity of construction brings the cost of repair to a minimum.

MATERIAL AND METHOD OF STUDY

Forty-four children, seven to sixteen years of age, presenting unequivocal evidence of acute rheumatic carditis were treated in the oxygen chambers for variable periods of time. All patients in this group had clear clinical evidence of mitral disease; three of these had, in addition, evidence of aortic insufficiency and ten had aortic stenosis and insufficiency. The majority of children had moderately enlarged hearts; many had subjective evidence of cardiac insufficiency and some had obvious signs and symptoms of congestive heart failure. All patients presented both clinical and laboratory evidence of rheumatic activity;[14] some were treated at the onset of the rheumatic episode, others many months after the onset; some presented "exudative" rheumatic manifestations while others had many of the "proliferative" phenomena.

Duration of residence in the oxygen chamber varied from twenty-four hours to forty weeks. Only three of the children were treated for less than one week; the average period of treatment was about twelve weeks and the majority of children received more than ten weeks of oxygen therapy. Each patient in this group was observed for a period of not less than two weeks prior to treatment and for many weeks or months following therapy. Oxygen therapy was continued uninterruptedly day and night, None of the children was removed from the oxygen chambers during the entire period of residence except on rare occasions for roentgenographic studies. All other laboratory and clinical procedures were carried on in the chambers. Residence in oxygen was continued until there was definite evidence of success or failure of this form of therapy except when the patient demonstrated unequivocal symptoms of intolerance to high concentrations of oxygen. In most cases residence in the chamber was discontinued gradually by increasing daily the period of residence outside of the chamber.

Great care was taken in keeping the oxygen concentration constant at a level of 45 to 50 per cent. The fluctuation was at no time greater than 5 per cent day or night (two-hour recordings were kept). The temperature was kept constant at a level of 66 to 68°F. and the humidity fluctuated between 60 and 70 per cent. The barometric pressure did not differ from that recorded outside of the oxygen chambers. Carbon dioxide concentration was permitted to rise to a level of 1.3 to 1.5 per cent. During the course of this study no attempt was made to lower the carbon dioxide concentration.* Preliminary studies were made upon the bacterial content of the oxygen chambers. No significant bacterial findings were noted as to number and type.

Other forms of cardiac therapy were instituted only when urgently indicated. Salicylates were withheld except in frank polyarthritis with pain. The diet did not differ in any respect from the usual well balanced diet given to all other patients at the sanatorium. Patients received the usual nursing care and every attempt was made to avoid emotional disturbances. In most instances these patients were unaware that they were receiving oxygen therapy. Frequent and detailed observations were made to evaluate the clinical behavior of the patient, auscultatory changes in the heart, effect upon venous pressure, blood circulation time, respiration mechanism and the progress of rheumatic activity.

* Earlier observations corroborated the suggestion of Henderson and his associates[15,18] that the inhalation of carbon dioxide above 1 per cent causes stimulation of the respiratory center and deeper respiration and thereby increases the effectiveness of oxygen inhalation.

RESULTS

Classification of Cases. Early in the course of this study it became clear that patients observed under treatment fell into three distinct groups:* (1) those who seem to react favorably to oxygen therapy, (2) those who were not benefited and (3) those who showed marked intolerance to this form of therapy. The difference in reaction to oxygen therapy in these three groups was striking. Of the forty-four children studied, three were intolerant to oxygen, seventeen did not show any improvement and twenty-four showed palpable to striking improvement under oxygen therapy. Further observation demonstrated clearly that these three groups of patients differed in important clinical respects:

1. "*Responsive*" *Cases:* Twenty-four of the forty-four patients showed definite improvement as a result of oxygen therapy. On admission to oxygen therapy, all of these children had auscultatory signs of valvular disease and all showed impressive evidence of acute rheumatic carditis. Some showed other exudative manifestations, polyarthritis, arthralgia, erythemas, pleuritis, etc. Symptoms of cardiac insufficiency, i.e., dyspnea, easy fatigability, etc., seemed to express the functional disturbance of the acutely inflamed heart rather than mechanical disability resulting from previous bouts of carditis. Some patients had low grade fever. The erythrocyte sedimentation rate was elevated in most of these cases and the hemoglobin was depressed. The heart was tumultuous and the cardiogram showed moderate to marked prolongation of the electrical systole.

2. "*Unresponsive*" *Cases:* Seventeen of the forty-four treated children were not benefited by oxygen therapy. Most of these were advanced cardiacs with a long-standing carditis and evidence of minimal or severe heart failure. Most of these children showed evidence of the proliferative phase of rheumatic disease (nodules). The cardiac disability was of long standing. All of these children had moderate or marked hypertrophy of the heart and well established valvular defects of long duration. In addition, most of these children from time to time showed other visceral manifestations of rheumatic disease: hepatic enlargement without evidence of right heart failure; pulmonary signs: pneumonitis, pleuritis or pneumonia and occasionally gastrointestinal manifestations.

Few of these children showed the usual laboratory evidence of rheumatic activity. The hemoglobin was not depressed. The erythrocyte sedimentation rate was elevated only slightly in one-half of the patients. The white blood count was normal. The temperature was low grade or normal. On the other hand, both clinically and cardiographically, all of these children showed unequivocal evidence of carditis. The heart was unstable and tumultuous and the murmurs and sounds were ever changing.

These patients then were advanced rheumatic cardiacs showing clinical evidence of the proliferative phase of rheumatic disease, marked mechanical cardiac disability and exudative phenomena of lesser degree.

3. *Group Showing Intolerance to Oxygen Therapy:* The three children who could not tolerate oxygen therapy belonged to the "bronchitic" type of rheumatic carditis. The musical râles in the chest were constant and widespread. An allergic etiology in this group cannot be ruled out. Our experience, however, leads to the impression that this manifestation is part of the picture of rheumatic activity rather than intercurrent allergic disease. Children having rheumatic carditis and evidence of widespread bronchitis present an unfavorable prognosis as to life and degree of cardiac damage. They do not react favorably to any form of therapy during the active phase of rheumatic disease. They are intolerant to salicylates and are markedly sensitive to digitalis therapy during the phase of congestive failure.

* Groups 1 and 2 will be referred to as "responsive" and "unresponsive" cases in this paper.

When these children are introduced into a 50 per cent oxygen atmosphere, they rapidly begin to develop respiratory difficulty. Within several hours, respiration becomes difficult and asthmatic in type. The rate of respiration increases and the musical râles in the chest may be heard without the aid of the stethoscope. Within a short time, the patient becomes dusky in color and soon becomes cyanotic. The heart rate rises and the patient becomes restless and anxious. Removal from the oxygen chamber at this point gives almost immediate and complete relief from respiratory difficulty. The heart rate slows rapidly. Restlessness and anxiety subside at once.

Of the three children who presented this manifestation, the longest period of residence in oxygen was three days and the shortest three hours. In one instance repeated attempts were made to introduce the child into the oxygen chamber with the same unfavorable results.

TABLE I
OXYGEN THERAPY IN RHEUMATIC CARDITIS IN CHILDREN

	"Responsive" Cases	"Unresponsive" Cases
Cases treated		
Number of cases	24	17
Average age for group	11 yr.	10 yr.
Average period of observation	9 mo.	11.5 mo.
Average period of O_2 therapy	12 wk.	15 wk.
Anatomic Diagnosis MI	0	2
Anatomic Diagnosis MSI	15	8
Anatomic Diagnosis M and A	7	7
Results—number of cases showing:		
1. Clinical improvement		
Drop in temperature	24	0
Drop in respiration	24	5
Weight gain	22	0
Increase in appetite	24	17
Improved facial coloring	24	0
Change in behavior pattern	20	2
2. Change in cardiac manifestations:		
Drop in pulse rate	24	4
Sounds and murmurs	24	2
Angina	6 of 7	2 of 3
Cardiac fatigue	6 of 7	4 of 11
Cardiac insufficiency (subj.)	12 of 13	5 of 7
Heart failure	.	0
ECG changes	16 of 17	Digitalis?
3. Increase in diuresis	24	0

Effect of Oxygen Therapy. The effect of oxygen therapy was studied from three points of view: (1) the clinical progress of the patient, (2) cardiac manifestations and (3) the progress of rheumatic activity. (Tables I and II.)

1. *Clinical Progress of Patients—Fever:* All the children who showed definite clinical improvement in the oxygen chambers showed a significant drop in temperature. This drop occurred within twenty-four hours of admission in eighteen of the twenty-four patients in this group. The remaining children showed a drop in temperature in four days except in one patient in whom the low grade fever persisted for two weeks. The drop in temperature was in the main either from a low grade fever to normal or from a high normal to a low normal level (99.2°F. to 97.6°F..) All patients showed a significant narrowing of the daily temperature fluctuation. In the "unresponsive" group of children the temperature did not drop from the original level and the daily fluctuation remained unchanged. (Figs. 2 and 3.)

Respiration: Twenty of the twenty-four "responsive" patients showed immediate improvement in respiration. Slowing of the respiratory rate and the relief in dyspnea occurred in most patients within the first twenty-four hours of residence in the oxygen chambers when the evidence of acute carditis and depletion of cardiac reserve (increased venous pressure, prolonged blood circulation time, etc.) remained unaltered. In the remaining four patients the respiratory rate dropped slowly but the depth of respiration increased within the first twenty-four to forty-eight hours of residence in oxygen.* Of the seventeen "unresponsive" patients only five showed a slight and temporary improvement in respiration; seven

* This change in respiratory mechanism is now under study.

TABLE II
"RESPONSIVE" GROUP

Patient	Before Oxygen Therapy													During Oxygen Therapy											
	Manifestations of Rheumatic Activity													Manifestations of Rheumatic Activity											
	Clinical						Acute Carditis							Clinical						Acute Carditis						
	Skin	Joints	Other	Fever	ESR	VC%	Tachycardia	Sounds and Murmurs	Fatigability	Angina	ECG	Cardiac: Insuf.	Cardiac: Failure	Skin	Joints	Other	Fever	ESR	VC%	Tachycardia	Sounds and Murmurs	Fatigability	Angina	ECG	Cardiac: Insuf.	Cardiac: Failure
A. H.	+	..	..	−	−	−22	−	+	....	++	+	+	..	+	..	..	−	−	−15	−	−	..	+	−		
B. R.	..	..	..	+	−	−45	+	+	+	....	+	+	..	....	..	..	−	−	−30	−	−	..	..	−	−	
C. M.	+	..	..	+	+	−40	+	+	+	..	+	+	..	++	..	..	−	−	−15	−	−	−	..	−		
C. V.	..	..	..	+	−	−40	+	+	....	....	+	..	..	....	..	..	−	−	−20	−	−	..	..	−		
C. H.	..	+	..	+	+	−35	+	+	....	....	+	..	..	....	+	..	−	+	−22	−	−	..	..	−		
F. A.	..	..	..	−	−	....	+	+	....	....	+	..	..	....	..	..	−	−	....	−	−	..	..	−		
G. E.	..	+	+	+	+	−40	+	+	+	+	..	..	..	....	+	+	−	+	−30	−	−	−	..	−		
G. G.	..	..	..	−	+	−22	+	+	....	....	+	..	..	....	..	..	−	+	−20	−	−	..	..	−		
G. S.	..	..	..	+	+	−40	+	+	+	+	Dig.	+	..	....	..	..	−	−	−20	−	−	−	−	Dig.	−	
S. A.	..	..	..	+	−	−35	+	+	....	....	+	+	..	....	..	..	−	+	−10	−	−	..	..	−	−	
I. R.	..	..	..	−	+	−15	−	+	....	....	+	..	..	....	..	..	−	+	+ 5	−	−	..	..	−		
L. J.	+	..	..	+	+	−50	+	+	....	....	Dig.	+	..	+	..	..	−	+	−40	−	−	..	..	Dig.	−	
J. V.	..	..	..	−	+	−50	−	+	....	....	+	+	..	....	..	..	−	+	−30	−	−	..	..	−	−	
Q. F.	..	..	..	−	+	−22	+	+	....	....	+	..	..	....	..	..	−	−	− 5	−	−	..	..	−		
R. G.	..	..	..	+	+	....	+	+	+	+	+	+	..	....	..	..	−	−	....	−	−	−	..	..		
R. G.	..	..	..	+	−	−40	+	+	+	++	+	+	..	+	..	..	−	−	−20	−	−	−	..	−	−	
R. R.	..	..	..	+	+	−50	+	+	....	....	..	+	..	....	..	..	−	+	−20	−	−	..	..	−		
R. R.	..	..	..	+	−	−20	+	+	....	....	..	..	..	....	..	..	−	−	−15	−	−	−	..	−	−	
R. B.	..	..	..	−	−	−40	+	+	+	....	Dig.	+	..	....	..	..	−	−	−40	−	−	−	..	Dig.	−	
S. T.	..	..	..	−	+	−20	+	+	....	....	+	..	..	....	..	..	−	+	0	−	−	..	..	−	−	
S. P.	..	..	..	−	−	−40	+	+	....	....	+	+	..	....	..	..	−	−	0	−	−	..	..	−		
S. J.	+	..	..	+	+	−25	+	+	....	+	+	..	..	−	..	..	−	−	−20	−	−	..	−	−		
S. J.	+	+	+	−	−	−25	−	+	....	+	+	+	..	+	+	+	−	+	−20	−	−	..	−	−	−	
V. M.	..	..	..	−	+	−40	+	+	....	....	Dig.	+	..	....	..	..	−	+	−40	−	−	−	..	Dig.	+	
No. of Cases Changed	5	3	2	13	14	....	20	24	7	7	17	13	0	5	3	2	0	10	....	0	0	0	1	0	1	
	..	..	..	..	..	....	..	..	....	....	..	..	..	0	0	0	24*	4	15	20	24	7	6	16	12	

TABLE II—*Continued*

"UNRESPONSIVE" GROUP

Patient	Before Oxygen Therapy													During Oxygen Therapy											
	Manifestations of Rheumatic Activity													Manifestations of Rheumatic Activity											
	Clinical						Acute Carditis							Clinical						Acute Carditis						
	Skin	Joints	Other	Fever	ESR	VC%	Tachycardia	Sounds and Murmurs	Fatigability	Angina	ECG	Cardiac		Skin	Joints	Other	Fever	ESR	VC%	Tachycardia	Sounds and Murmurs	Fatigability	Angina	ECG	Cardiac	
												Insuf.	Failure												Insuf.	Failure
A. L.	+	..	..	−	−	....	+	+	+	....	Dig.	+	+	+	..	..	−	−	− 5	+	+	−	..	Dig.	−	+
A. A.	..	..	..	−	−	−40	+	+	....	....	..	+	..	....	..	..	−	−	0	+	+	..	..	..	−	
B. H.	+	..	..	−	−	−50	+	+	....	....	+	+	+	+	..	..	−	−	−50	+	+	..	..	Dig.	+	+
DeM. C.	..	..	..	−	−	−40	+	+	....	....	Dig.	+	+	....	..	..	−	−	−18	−	−	..	..	Dig.	−	−
F. R.	+	+	..	+	+	−40	+	+	+	+	+	+	+	++	+	..	+	+	−40	+	+	+	+	Dig.	+	+
F. L.	+	..	..	−	+	−50	+	+	+	+	Dig.	+	+	+	..	..	−	+	−50	+	+	+	−	Dig.	+	+
L. E.	+	..	..	−	+	−40	+	+	+	..	+	++	+	++	..	..	−	+	−20	+	+	+	+	Dig.	+	+
M. A.	+	..	..	−	+	−40	+	+	+	..	+	+	..	+	..	..	−	−	−35	+	+	−	..	+	+	
O'C. M.	+	..	..	+	−	−45	+	+	+	..	Dig.	+	+	+	..	..	+	−	−45	+	+	−	..	Dig.	+	+
P. M.	..	..	..	+	−	−40	+	+	+	..	Dig.	+	+	..	..	..	+	+	−30	+	+	+	..	Dig.	+	+
P. B.	+	..	..	+	+	−40	+	+	....	....	+	+	..	+	..	..	+	−	−40	−	+	..	..	+	+	
P. S.	+	..	..	−	−	−40	−	+	+	..	+	+	+	+	..	..	−	−	−40	−	+	+	..	+	+	
R. G.	+	..	..	+	−	−40	+	+	++	....	Dig.	+	−	+	..	..	+	+	−35	+	+	−	..	Dig.	−	+
R. G.	+	..	+	−	+	−45	+	+	++	....	+	+	+	+	..	..	−	−	−50	+	+	+	..	+	+	+
R. P.	+	..	..	+	+	−50	+	+	+	+	Dig.	+	+	++	..	..	+	−	−50	+	+	+	−	Dig.	+	+
S. Z.	+	..	..	−	−	−40	+	+	..	..	Dig.	+	+	+	..	..	−	−	−40	+	+	+	+	Dig.	+	+
M. E.	+	..	..	−	+	−40	−	+	..	..	Dig.	+	++	+	..	..	−	+	−40	−	−	..	..	Dig.	−	+
No. of Cases	14	1	1	6	8	....	15	17	11	3	7	17	13	14	1	0	6	6	....	13	15	8	3	4	12	13
Changed	..	..	..	..	..	....	..	..	....	....	..	..	..	0	0	1	0	2	3	2	2	4	2	3	5	0

\+ = the presence of abnormal signs or symptoms.
− = the absence of abnormal signs or symptoms.
Skin = rheumatic erythemas and rheumatic nodules.
Joints = polyarthritis or persistent joint pains.
Other = epistaxis, progressive pallor, abdominal pain, etc.
* Fever = thirteen patients had fever and twenty-four patients showed a drop in temperature either from fever or from a normal level in the "responsive" group.
ESR = + elevated and − normal sedimentation rate.
VC% = the percentage of normal for body surface (vital capacity).
Tachycardia = a rate of 115 or more.
Sounds and murmurs = frequent changes of sounds and murmurs.
Cardiac insufficiency = subjective signs such as dyspnea.
Cardiac failure = objective signs of congestive heart failure: râles in the chest, edema, enlarged liver, increased venous pressure, etc.
ECG = + signifies electrocardiographic deviations from the normal and − signifies no such deviations.

children had no relief from dyspnea, orthopnea or tachypnea and five children showed a moderate increase in respiratory rate. There was no increase in depth of respiration in any of the children in this group.

status or the downward course of the disease. Some children who suffered from acute pancarditis with frank congestive failure had an inordinate increase in appetite during their residence in the oxygen chambers. In this group the appetite

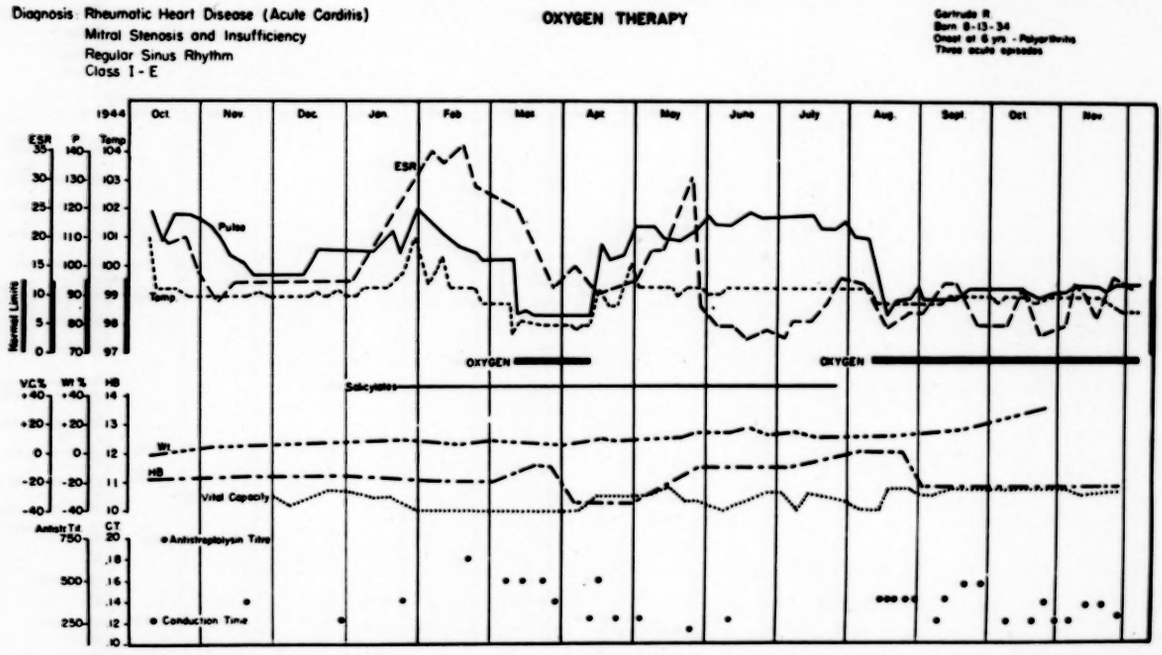

FIG. 2. Chart showing the effect of oxygen therapy upon the clinical course of acute rheumatic carditis. The temperature and pulse curves are smoothed.

*Weight Gain:** Of the twenty-four "responsive" patients, twenty-two gained weight at a greater rate than would be expected in a similar group of children with carditis treated routinely outside of the oxygen chamber. The majority of these children began to add weight within one week after oxygen therapy was begun. These showed no such gain for many weeks preceding oxygen therapy. In the "unresponsive" group less than one-half[7] gained slight weight at a slow rate; six children failed to gain during the entire period of observation and four lost a significant amount of body weight.

Appetite: A marked increase in appetite was a common finding among all children who resided in the oxygen chambers. In some instances the increase in appetite was enormous irrespective of the cardiac failed when oxygen therapy was terminated. In the group of children who improved with oxygen therapy, appetite also decreased when the therapy was stopped, but to a lesser degree than in the "unresponsive" patients.

Complexion: Most children residing in the oxygen chambers showed improvement in facial coloring. This was a late manifestation and did not seem to be related to the changes in hemoglobin level. Facial coloring improved at the time when the hemoglobin level was dropping. In the "responsive" group of patients the increase in facial coloring was often marked although the hemoglobin was dropping. In the "unresponsive" group the improvement in facial coloring was slight and temporary although the hemoglobin level in this group was not depressed.*

* Weight gain is referred to as "dry weight" and not edema.

* Changes in hemic components during resistance in 50 per cent oxygen will be discussed in subsequent studies.

Behavior: The "responsive" group of children showed an obvious and significant change in their behavior pattern almost as soon as they were introduced into the oxygen chambers. Irritability, nervousness, impatience and capriciousness changed to obvious contentment, cheerfulness and a sense of peacefulness in most cases within the first twenty-four hours of residence in oxygen. In this group a sense of well being was observed out of proportion to the degree of cardiac disability. While personality differences obviously play an important rôle in adaptation to the discomforts of illness, it is clear from our observations that all children who are benefited by oxygen therapy show an apparent sense of well being as soon as oxygen therapy is instituted. This change in the behavior pattern was not observed among the "unresponsive" group of children. Impatience, resistance to therapy, inimical relationship to doctors and nurses continued unchanged. In this group the degree of emotional upheavals was in the main proportional to the extent of cardiac disability, multiplicity of symptoms and the degree of rheumatic activity.

2. *Cardiac Manifestations—Pulse Rate:* Twenty of the twenty-four "responsive" patients showed a rapid and dramatic drop in pulse rate. The rate dropped from a moderate tachycardia of 110 to 130 to the normal level of 70 to 90 within twenty four hours of admission to the oxygen chamber. In the other four patients the drop in pulse rate was delayed for several days. The drop in pulse rate was constant and remained at a low level during the entire period of residence in the oxygen chamber. The advent of an intercurrent infection or rheumatic recrudescence raised the pulse rate level only slightly. Emotional disturbance did not disturb the slow pulse rate to any significant degree. The labile character of the pulse rate commonly observed in rheumatic carditis changed to definite stability in this group of patients shortly after the institution of oxygen therapy; the fluctuation in pulse rate was rarely more than ten points. The stability of the pulse rate continued in all cases after oxygen therapy was discontinued. In the "unresponsive" group of patients there was no drop of pulse rate after oxygen was begun. In some of these children there was actually a temporary rise in the heart rate during the first three to six days of residence in oxygen. In a few the pulse rate dropped slightly during the first four days of treatment. The daily fluctuation remained unchanged in the entire group. The labile character of the pulse rate remained unaltered.

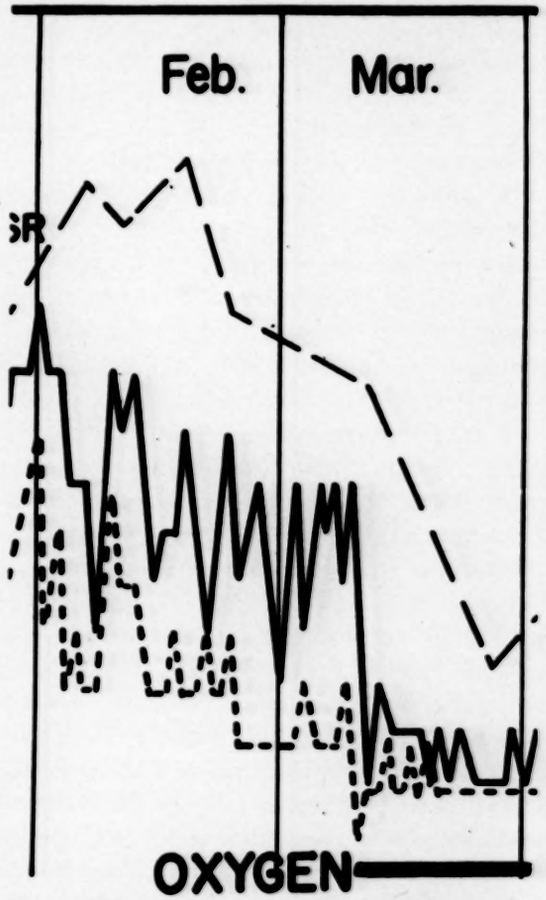

FIG. 3. This is a photographic representation of the temperature and pulse rate chart during the months of February and March. Note the marked fluctuation before oxygen therapy was begun and the minimal fluctuation during therapy.

Clinical Carditis[14]*—"Responsive" Cases:* Of the twenty-four children in this group, twenty-two showed measurable improvement in the functional disturbance of the

acutely inflamed heart during oxygen therapy. Tachycardia, gallop rhythm, tumultuous character of heart action and instability of cardiac rate gradually subsided. While it cannot be said with any degree of assurance that oxygen influenced the course of carditis in this group, functional cardiac disturbances usually associated with acute carditis subsided in this group of patients in a shorter period than would be expected for a similar group of patients outside the oxygen chamber.

"*Unresponsive*" *Cases:* Of the seventeen children in this group only two showed similar improvement shortly after admission to the oxygen chamber. The remaining fifteen showed no such improvement and some indeed showed evidence of increase in severity of cardiac disability.

Murmurs—"*Responsive*" *Cases:* The frequent changes in quality and mode of transmission of murmurs during the course of acute carditis is well known. In six of the twenty-four children in this group, mitral diastolic murmurs which were heard for long periods of time prior to residence in the oxygen chamber completely disappeared and were not heard for the entire period of observation. In one instance an aortic diastolic murmur disappeared at the end of the period of residence in the oxygen chamber. In a few children of this group the murmurs remained unaltered and in one child evidence of aortic insufficiency developed during the conrse of treatment. The duration of time during which these auscultatory changes took place varied greatly from patient to patient. In some instances it took many weeks before such changes were effected and in most instances it seemed as if these changes occurred *pari passu* with the cessation of carditis. On the other hand, in several patients these changes took place shortly after oxygen therapy was instituted.

It cannot be stated at this time that these auscultatory changes resulted from the effects of oxygen therapy or were manifestations of the natural course of the progress of acute carditis. It is clear, however, that these changes were observed more frequently than was found to be the case, in our experience, in a similar group of children treated outside of the oxygen chambers.

"*Unresponsive*" *Cases:* In this group of children no auscultatory changes were noted. One child developed a definite mitral stenosis while under treatment; one aortic insufficiency and one tricuspid stenosis.

Anginal Syndrome: Seven children had repeated attacks of anginal pain before oxygen therapy was instituted. The precordial pain was of sudden onset, radiating to shoulders and arms, associated with a sense of anxiety and in most instances was relieved rapidly by the administration of nitroglycerin. In all patients in whom cardiograms were taken during the attack, evidence of anoxemia was noted (depression of S-T segments and T wave changes). Some of these subjects had a marked rise in systolic pressure during the anginal seizure and a marked tachycardia.

All these children showed significant relief from these attacks during residence in oxygen. In some instances the seizures persisted but were of a distinctly milder type. The pain was minimal and the tachycardia somewhat controlled although the associated rise in systolic pressure remained unaltered. None of these children demonstrated the sense of anxiety which was obvious before oxygen therapy was instituted. Six of the seven patients in this group had complete and permanent cessation of this syndrome within one to ten weeks of the onset of oxygen therapy. In one instance several anginal attacks were observed a few weeks after residence in oxygen was discontinued.

Cardiographic Changes—Conduction Disturbances:* In the "responsive" group of patients

* In this study cardiographic changes of three sorts are considered: (1) disturbance in conduction; (2) changes commonly considered indicative of cardiac anoxemia, i.e., S-T segment deviations and temporary T wave changes and (3) changes which we consider as significant of impairment of the integrity of the heart muscle, i.e., prolongation of the electrical systole (Q-T interval).

conduction disturbance observed on the cardiogram subsided rapidly under the influence of oxygen therapy. One child in this group showed a Wenckebach type of block which disappeared within twenty-four hours of residence in oxygen. On the other hand, most of the children in the "unresponsive" group demonstrated conduction disturbances of one sort or another during the course of observation. These disturbances did not seem to be influenced by oxygen therapy. No conclusion, however, can be drawn from this observation since all the children in the latter group were receiving digitalis therapy in addition to oxygen therapy.

Anoxemia Changes: Four children of the "responsive" group showed significant deviations in the S-T segment before admission to the oxygen chambers. All of these deviations subsided within a short period of residence in an oxygen atmosphere. Two of these children showed minimal S-T deviations as soon as oxygen therapy was terminated and in one instance these changes were associated with attacks of precordial pain of an anginal type. In the "unresponsive" group of children S-T and T changes could not be evaluated since these children were digitalized and continued on a maintenance dose during the entire period of observation.

Changes in the Duration of Electrical Systole[17] *(Q-T Interval):* All children of the "responsive" group had prolonged Q-T intervals at the time oxygen therapy was begun. Many showed a shortening of the Q-T intervals at the end of the period of treatment. Others continued to have prolonged Q-T intervals for weeks and months following oxygen therapy. The shortening of the Q-T interval ran parallel to the subsidence of acute carditis and did not reflect the effect of oxygen therapy upon cardiac efficiency. That digitalis shortens the Q-T interval is well known. Many of the "unresponsive" group of patients were receiving digitalis. Therefore, the effect of oxygen therapy upon the Q-T interval in this group could not be studied.

Diuresis: All children in the "responsive" group showed some increase in diuresis shortly after treatment was begun. In the "unresponsive" group no increase in diuresis was observed. On the contrary the rapidly advancing signs of failure necessitated the active use of mercurials or other diuretics. Furthermore, oxygen therapy did not enhance the diuretic effect of mercurials or digitalis.

3. *Progress of Rheumatic Activity.* The natural history of rheumatic disease does not seem to be significantly altered by prolonged residence in 50 per cent oxygen. Clinical and laboratory evidence of active rheumatic disease continued unabated in the "responsive" and "unresponsive" groups of patients. Many of the clinical manifestations of acute rheumatic fever, i.e., polyarthritis, erythema marginatum, nodules and epistaxis recurred from time to time during the entire period of residence in the oxygen chambers in both groups of children. In the "responsive" group of children, however, rheumatic bouts (joint and skin manifestations, epistaxis, etc.) were not accompanied by an increase in pulse rate, in the tumultuous character of the heart rhythm and by electrocardiographic changes to the same extent as was observed in a similar group of patients not receiving oxygen therapy.

COMMENTS

The primary aim in the treatment and management of rheumatic fever is the prevention of progressive cardiac damage during the course of acute carditis. To this end various forms of therapy have been advocated: prolonged bed rest, sedation, cardiac supportive medication, carefully controlled sanatorial and convalescent care and limitation of physical activities of one sort or another for long periods of time. It must be admitted that despite all such efforts a large group of children suffering from acute rheumatic carditis present greatly damaged hearts at the end of the acute episode. This damage is attributed to a failure to attain effective cardiac rest

during the course of the acute inflammatory process of the myocardium. It is thought that even under the best physical and emotional environment of rest and relaxation the heart muscle is overactive in acute carditis. Overactivity of the acutely inflamed muscle fiber may be responsible for disturbance of the chemical and mechanical integrity of the heart muscle fiber, causing dilatation and further impairment of cardiac efficiency. An accelerated cardiac action may further deplete cardiac efficiency by diminishing diastolic coronary filling, accentuating an already existing anoxemia of the heart muscle. Anoxemia of the heart muscle results in further disturbance of the metabolism of the muscle fiber.

It would seem reasonable to assume, therefore, that a form of therapy which diminishes cardiac overactivity during the course of the acute inflammatory process might prevent the damaging end result of acute carditis. A significant decrease in cardiac rate alone would undoubtedly diminish the work of the heart whose working capacity is already impaired by local tissue anoxia. Decrease in an accelerated cardiac rate might further improve the local tissue oxygen want by improving coronary filling. Finally, this form of therapy might in addition raise the oxygen saturation of the arterial blood which may be critically diminished in these patients.

The observations presented in this paper suggest that oxygen therapy seems to meet these requirements. Cardiac overactivity apparently is diminished. While the duration of rheumatic activity is not measurably shortened by oxygen therapy, the cardiac functional disability associated with acute carditis is greatly reduced. In addition it is obvious that residence in a high oxygen environment during the course of acute carditis removes the disabling and often most troublesome symptom of cardiac fatigue so commonly observed in children suffering from acute rheumatic carditis. The latter symptomatic relief enhances relaxation, sleep and nutrition, factors which undoubtedly contribute to rapid and satisfactory recovery.

Our experience further suggests that oxygen therapy is of only limited value in rheumatic heart disease of long standing, in which depletion of cardiac reserve presumably is caused mainly by mechanical deficiency of the heart as a pump. In these patients, previous repeated bouts of carditis has resulted in a markedly hypertrophied and dilated heart muscle with low cardiac reserve; the current acute rheumatic process in these patients is only contributory to the failure of a heart which already has a low reserve. Once the muscle fiber has become mechanically deficient, oxygen therapy is of limited value. This observation may explain, in part, the failure of oxygen therapy to produce favorable results in the type of rheumatic heart disease with congestive failure reported by Dr. Barach.[6a,b, and c] His patients may have been old rheumatic cardiacs with mechanically impaired hearts. Poulton, on the other hand, made his observations in children who had acute carditis. These may have belonged to the group of patients in whom functional cardiac disturbance of the heart was the dominant factor of cardiac disability. In these, oxygen therapy is effective.

SUMMARY AND CONCLUSIONS

1. Forty-four children suffering from acute rheumatic carditis were treated in a carefully regulated oxygen atmosphere of 45 to 50 per cent for long periods of time.

2. The clinical course of carditis was favorably affected in twenty-four of these patients; seventeen patients did not show measurable improvement with this form of therapy and three children showed marked intolerance to the oxygen therapy.

3. The three groups of patients differed clinically in important respects. Criteria for this differentiation have been described.

4. Our observations show that established cardiac damage cannot be reversed by oxygen therapy. They further show that the duration of rheumatic activity is not measurably altered.

5. Our results indicate, however, that oxygen therapy is an important form of treatment in acute rheumatic carditis of the exudative type with minimal mechanical cardiac disability. It reduces significantly the functional cardiac disability associated with acute carditis and favorably affects the clinical symptomatology toward more complete recovery.

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Effect of Oxygen Therapy on the Electrical Sequence of Events in the Cardiac Cycle in Children with Acute Rheumatic Carditis*

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In a previous communication[1] evidence was presented to show that in children the functional integrity of the heart muscle is impaired in acute carditis. It was further shown that the impairment is expressed in a disturbance of the normal time relationships in the electrical events in the cardiac cycle. The duration of electrical systole (Q-T) is increased both absolutely and relatively to diastole (T-Q). In other words, the duration of contraction† of the heart muscle is prolonged and the period of relaxation is shortened. It was further pointed out that this prolongation in contraction time reflects the degree of functional cardiac disability as measured by the usual clinical manifestations of acute heart disease. The more severe the carditis the longer the duration of systole ($Q\text{-}T_s$).

It was also noted that while the slowing of the speed of contraction may be an expression of the best cardiac effort under the adverse circumstance of the presence of an acute inflammatory process in the heart muscle, such a method of "compensation" is attended by a marked shortening of the period of cardiac relaxation. Diastole (the perfusion time during which chemical balance is restored) becomes abnormally short. A marked decrease in the perfusion time may produce a deficit in the chemical economy of the heart muscle. Thus, the prolongation of the period of contraction without a commensurate increase in the period of relaxation would seem to be an unprofitable physiologic compensation. The postulate was made that such a faulty cardiodynamic mechanism may contribute to the functional disability of the heart in acute carditis.

It would follow from this observation that a form of therapy which would bring about a normal relationship between the duration of active contraction and the duration of relaxation might restore a more profitable chemical economy in the heart muscle and prevent or reduce the cardiac functional disability of acute heart disease.

Several years' experience with use of oxygen in the treatment of rheumatic carditis in children strongly suggests that this form of treatment given during the exudative phase of acute carditis is an important form of therapy.[3] Our observations show that oxygen therapy does not alter the established anatomic cardiac damage but reduces significantly the cardiac functional disability which is present during the acute phase of the disease. There is a marked and rapid drop in heart rate and a decrease in respiratory rate. Precordial pain and evidence of cardiac fatigue subside. In some instances there is an increase in diuresis and a significant drop in the elevated venous pressure. The tumultuous character of the heart action is changed to a quiet and slow rhythm. In addition, the clinical behavior of the

† The electrical and mechanical systoles are considered from the clinical standpoint equivalent in this paper.[2]

* From the St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island, N. Y. This study was made possible through grants given by the Life Insurance Medical Research Fund and the Research Department of the Linde Air Products Company.

patient is profoundly changed in favor of a more complete recovery.

This marked clinical improvement in cardiac function prompted us to investigate the effect of oxygen therapy upon the electrical events of the cardiac cycle. The study of the relationship of systole to diastole in patients with acute carditis receiving oxygen therapy forms the thesis of this paper.

MATERIAL AND METHOD OF STUDY

Patients. Fifteen girls ten to fourteen years of age were chosen for this study. All these girls had unequivocal histories of rheumatic fever and during the period of observation had obvious clinical signs and symptoms of rheumatic carditis. Some presented symptoms of cardiac fatigue, others an anginal syndrome and some had incipient signs of heart failure. All patients exhibited the usual laboratory confirmatory evidence of carditis—an elevated sedimentation rate, a depressed hemoglobin and a low vital capacity reading. Several of the patients showed the usual changes on the electrocardiogram—disturbance in conduction and changes in the ST and T segments; all patients presented moderate to marked prolongation of the electrical systole ($Q\text{-}T_c$). None of these patients had obvious signs of heart failure during the period of study. Patients with acute pericarditis, marked nutritional disturbance, severe secondary anemias, allergic bronchitis or obvious disturbances in metabolism were excluded from this study.

During the entire period of observation no medication was given to these patients except an occasional sedative for angina or restlessness. None of these patients received digitalis for more than three weeks preceding the period of observation and none received diuretics. The diet was a normal well balanced diet with no salt or fluid restriction.

After a control period of study of not less than two weeks these patients were introduced into an oxygen chamber* where the oxygen concentration was 45 per cent to 50 per cent and the carbon dioxide concentration level fluctuated between 1 per cent and 1.3 per cent. During the control period complete studies were made to evaluate the degree of carditis, to establish a complete diagnosis and to rule out complications which might introduce new factors in this study. Complete studies were made within the first twenty-four hours after oxygen therapy was begun. Frequent and repeated observations were continued for the entire period of residence in the oxygen chamber.

Graphic Representation. The duration of electrical systole (Q-T interval) varies greatly with the length of the cardiac cycle. Therefore, in order to know whether a given Q-T interval is of normal length or not one must know what the normal length of electrical systole is for a particular rate. This is expressed in Bazette's formula:

$$K = \frac{\text{Q-T interval in seconds}}{\sqrt{\text{cardiac cycle in seconds}}}$$

K is the constant which expresses the corrected Q-T interval ($Q\text{-}T_c$) in terms of cardiac rate. It has been shown that the upper limit of normal $Q\text{-}T_c$ for a child is 0.405.[4] We have shown elsewhere[1] that in children with rheumatic carditis the prolongation of electrical systole (Q-T) bears a distinct relationship to the degree of disturbance in cardiac function resulting from carditis and not to the cardiac rate. In other words, the degree of disturbance in cardiac function in carditis is measured in the disturbed time relationship between systole and diastole. The longer the duration of systole as related to diastole the more severe the carditis.

In order to evaluate the severity of carditis in our patients treated with oxygen a graphic representation was made upon which was plotted the relationship of systole to diastole at varying cardiac rates and varying degrees of carditis as expressed by the prolongation of ($Q\text{-}T_c$. (Fig. 1.)

The ordinate represents varying quotients of $\frac{Q\text{-}T}{T\text{-}Q}$ as measured directly on the electrocardiogram. The abscissa represents cardiac rates ranging from 70 to 136. The curves on the graph were obtained by connecting multiple points representing the quotients of $\frac{Q\text{-}T}{T\text{-}Q}$ calculated for corrected Q-Ts (K)* ranging from 0.36 to 0.49 at cardiac rates ranging from 70 to 136. Thus, the quotient $\frac{Q\text{-}T}{T\text{-}Q}$ in a case of carditis with a corrected Q-T of 0.49 and a cardiac rate

* This chamber has been described elsewhere.[3]

* K and $Q\text{-}T_c$ are used interchangeably.

of 136 is 2.81. In the same patient with the same degree of carditis but at the cardiac rate of 70 the quotient is 1.15. The shape of the curves is explained in the following manner: the convergence of the curves at slow cardiac rates and the divergence of the curves at high

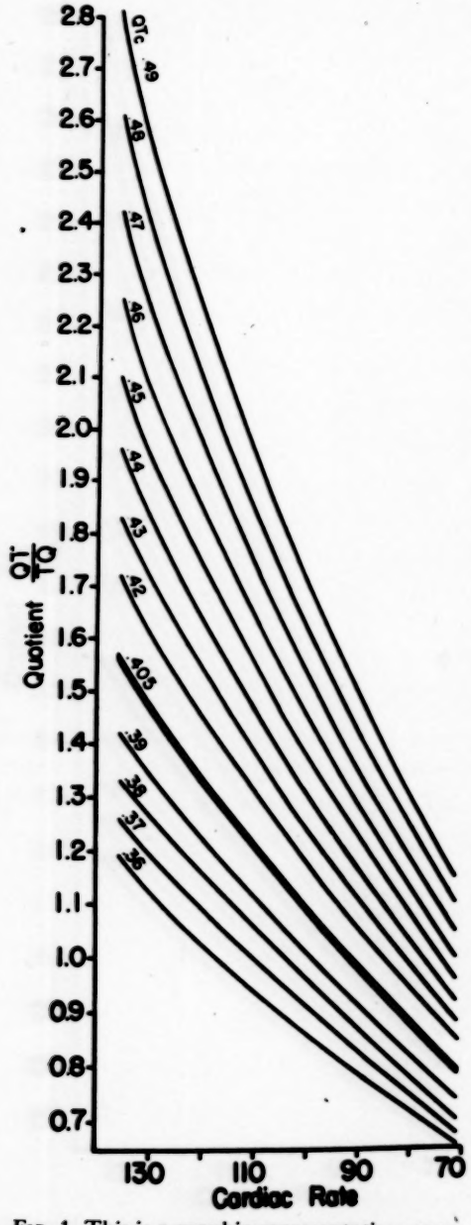

FIG. 1. This is a graphic representation upon which is plotted the relationship of systole to diastole at varying cardiac rates and varying degrees of carditis as expressed by the prolongation of the QT_c.

cardiac rates is derived from the nature of Bazette's formula since the significant change in the formula at various cardiac rates is the length of the cardiac cycle.

$$K = \frac{\text{Q-T in seconds}}{\sqrt{\text{R-R in seconds}}}$$

$$\text{Q-T} = K\sqrt{\text{R-R}}$$

$$\text{T-Q} = \text{R-R} - \text{Q-T in seconds;}$$

therefore,

$$\frac{\text{Q-T}}{\text{T-Q}} = \frac{K\sqrt{\text{R-R}}}{\text{R-R} - K\sqrt{\text{R-R}}} \text{ or}$$

$$\frac{K\sqrt{\text{R-R}}}{\sqrt{(\text{R-R})^2} - K\sqrt{\text{R-R}}} \text{ or } \frac{K}{\sqrt{\text{R-R}} - K}$$

The larger the K and the smaller the denominator the greater the quotient; the smaller the K and the larger the denominator the smaller the quotient.

RESULTS

All of the fifteen patients studied presented similar changes in regard to the relationship of systole to diastole shortly after oxygen therapy was instituted. (Figs. 2 to 17.) An analysis of these graphs will show that in each case cardiac rate was decreased and there was a rapid return to a more normal relationship of systole to diastole when oxygen therapy was begun. This was attained in all patients not by significant shortening of the systolic period (Q-T) but rather by a marked lengthening of the diastolic period (T-Q). In some instances the increase in duration of diastole was many times that of systole. This occurred in all cases irrespective of the time it took to effect the result after oxygen therapy was instituted.

In some cases this was attained within the first twenty-four hours of oxygen therapy; in others, a longer period was required to bring about a similar result. Those patients who showed evidence of myocardial damage such as deviations of the S-T interval and distortions in the T wave required a longer period of oxygen therapy before clinical improvement became manifest and a more normal relationship of systole to diastole was attained. In these cases the electrocardiographic signs of cardiac anoxia subsided first. In some, the electrical systole became longer as the S-T segments returned to the iso-electric

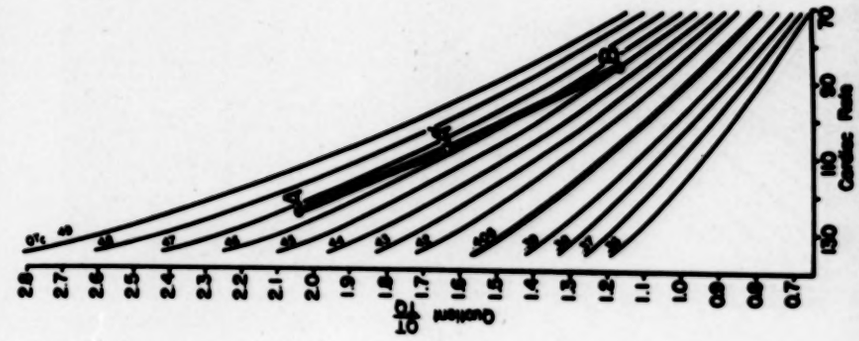

Fig. 2. Case 1

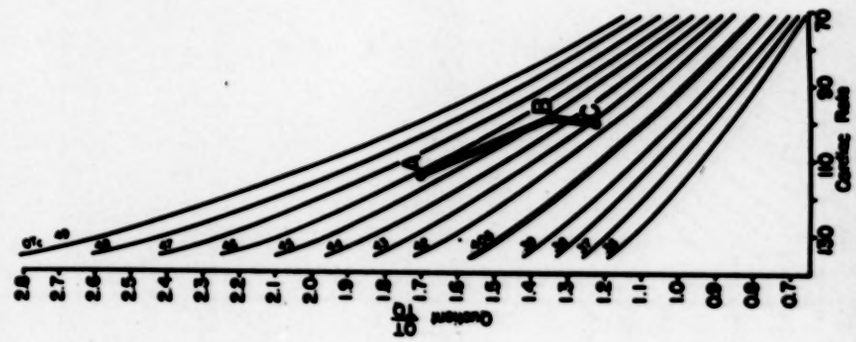

Fig. 3. Case 2

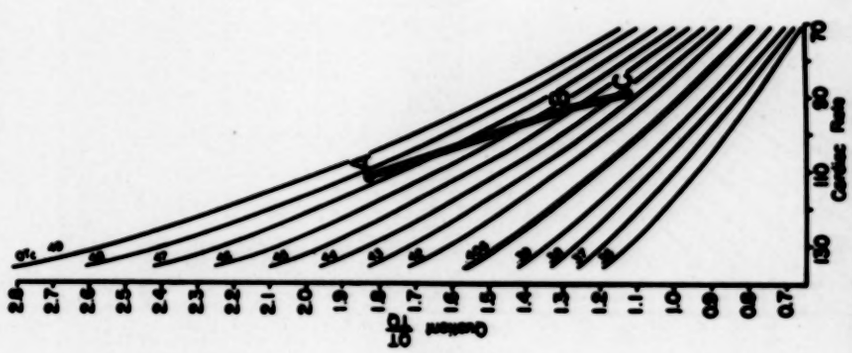

Fig. 4. Case 3

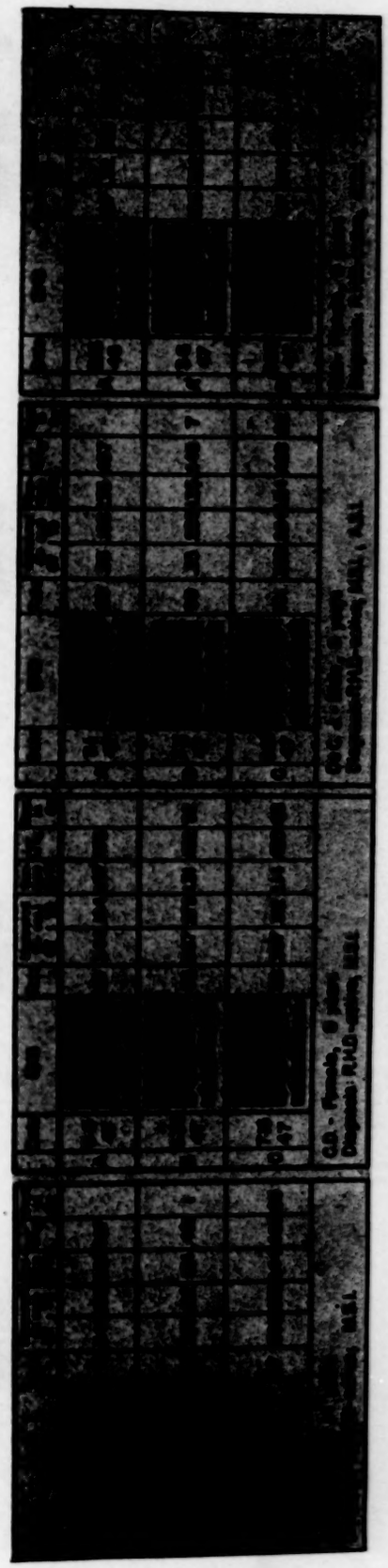

Fig. 5. Case 4

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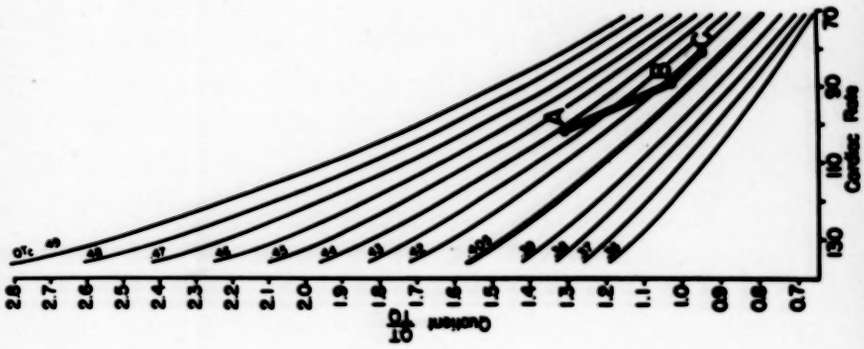

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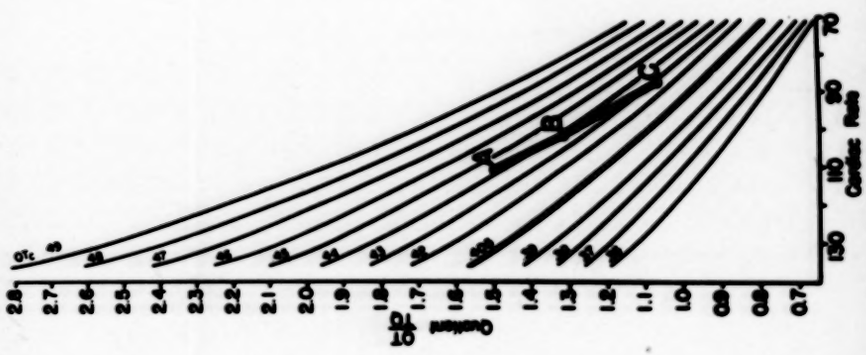

Fig. 7. Case 6

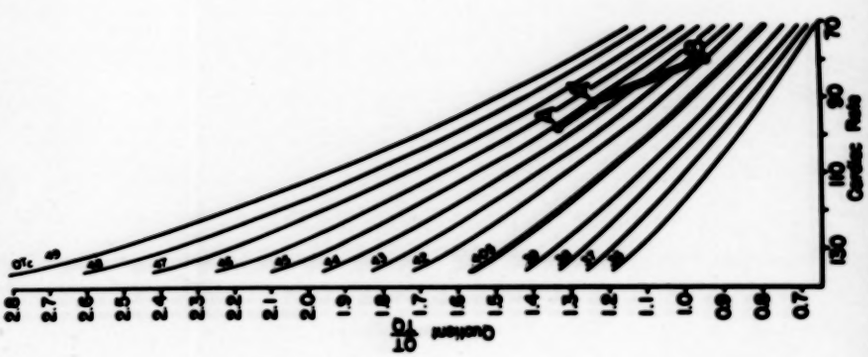

Fig. 8. Case 7

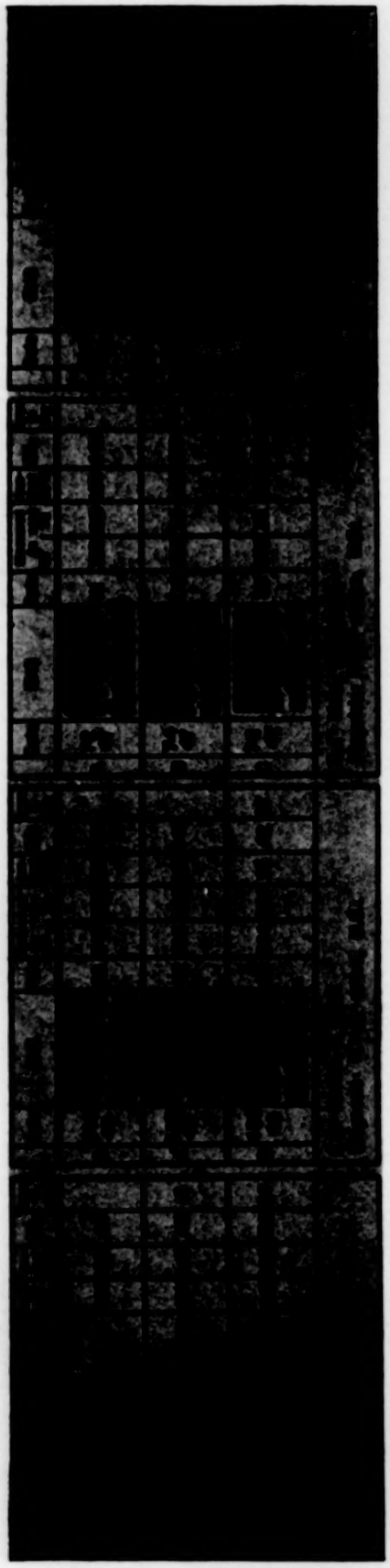

Fig. 9. Case 8

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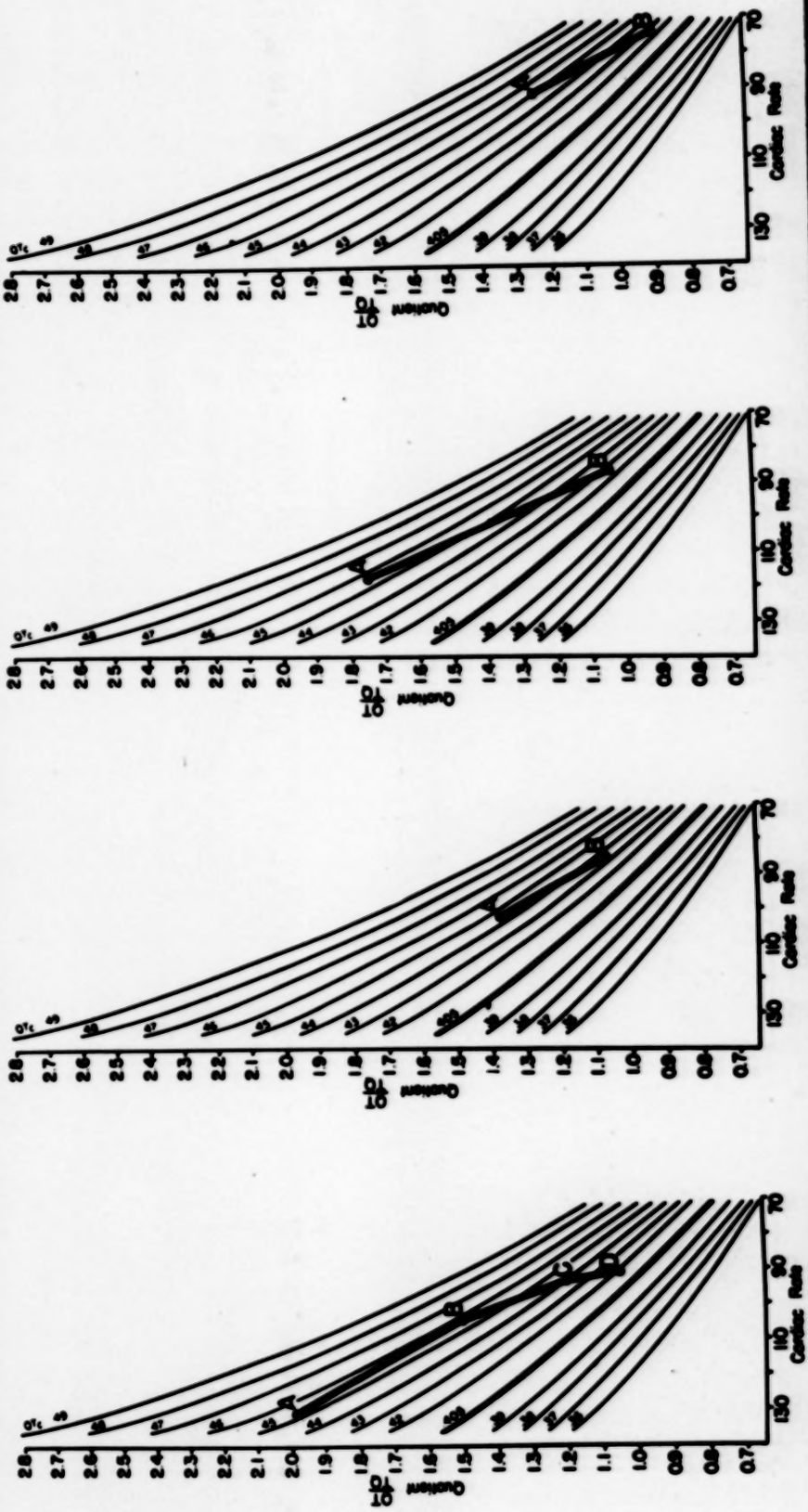

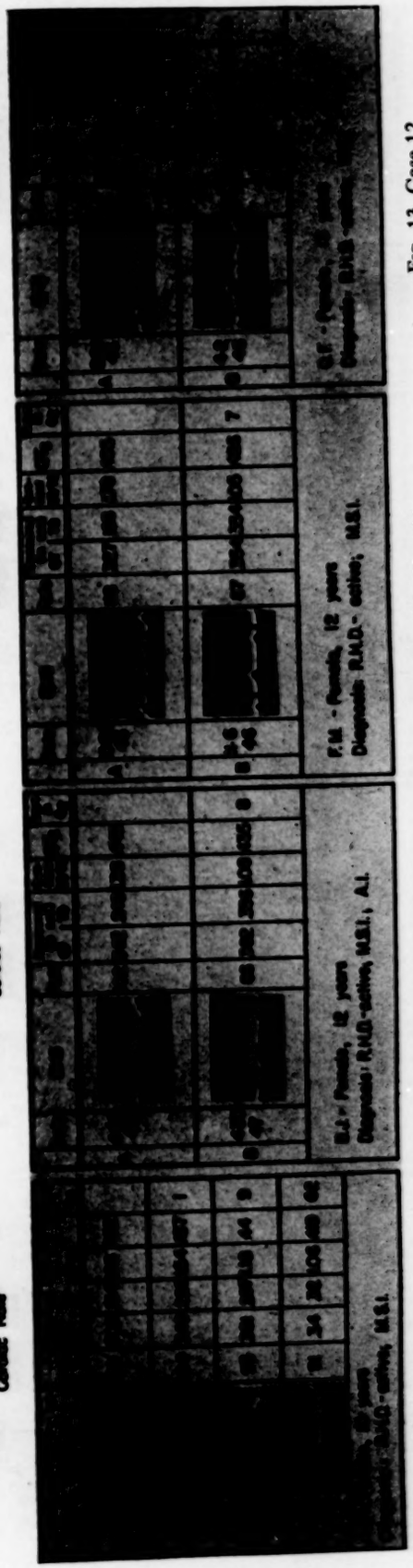

Fig. 10. Case 9

Fig. 11. Case 10

Fig. 12. Case 11

Fig. 13. Case 12

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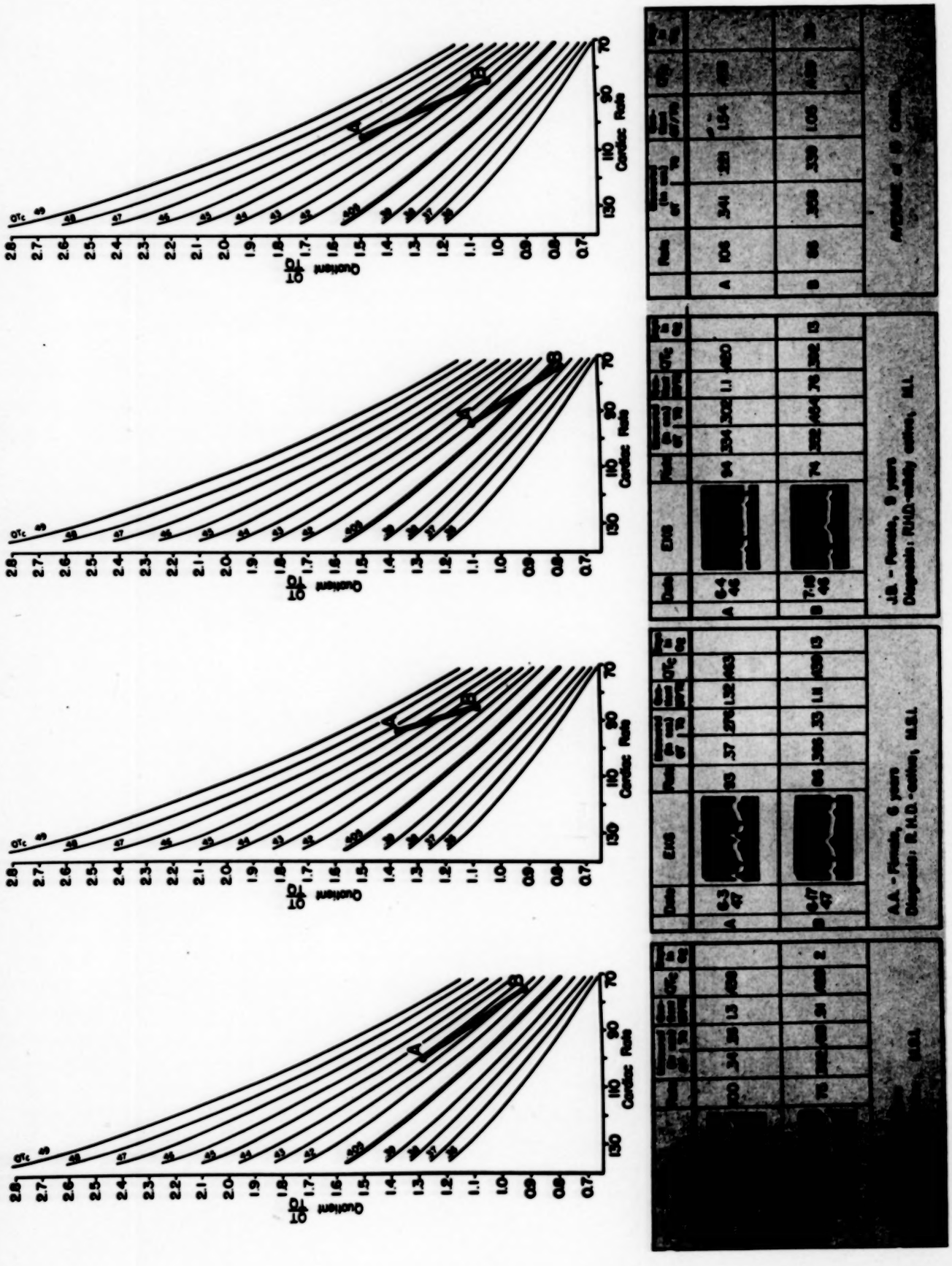

FIG. 14. Case 13

FIG. 15. Case 14

FIG. 16. Case 15

FIG. 17.

For legends see page 399.

FIGS. 2 to 16. Graphic representations of the change in electrical events within the cardiac cycle in each of the fifteen patients treated with oxygen during the course of acute carditis. The heavy curved line marked 0.405 represents graphically the $\frac{QT}{TQ}$ relationship at varying cardiac rates at a QT_c (K) of 0.405. All curved lines above this level represent abnormal $\frac{QT}{TQ}$ relationships found in cases of carditis; those below this level represent a normal $\frac{QT}{TQ}$ relationship found in normal children with quiescent rheumatic heart disease. The heavy lines connecting the open circle represent graphically the $\frac{QT}{TQ}$ relationship in each of our cases at several stages of therapy: (A) before oxygen; (A′) before oxygen therapy was started but at a later date; (B) shortly after oxygen therapy was begun; (C) after oxygen therapy was continued for a variable period of time; (D) at a still later date. A close analysis of these graphs shows the following:

1. In cases in which the rheumatic carditis continues the abnormal relationship of systole to diastole remains unaltered even though the heart rate may become slower. This is expressed in the fact that the QT_c remains unchanged. When such patients are introduced into a high oxygen atmosphere, the pulse rate may or may not drop further but there is a distinct change in the relationship between systole and diastole. This is attained primarily by a lengthening of the diastolic period. (See Case 4, Fig. 5 and Case 6, Fig. 7.)

2. The heart rate drops measurably shortly after beginning oxygen therapy in patients with carditis, but the relationship of systole to diastole as expressed in the QT_c may remain either completely unaltered or only slightly changed in the direction of normal. As oxygen therapy is continued for only a few days, the heart rate in most instances continues to decrease. The important change, however, occurs in the relationship of systole to diastole. The QT_c becomes shortened. This is attained by a marked prolongation of the diastolic period even at the time when the systolic period is either completely unchanged or only slightly prolonged. (See Figs. 2, 3, 6, and 8 to 16 inclusive.) In instances in which there is no drop in cardiac rate there is still a restoration to a more normal relationship of systole to diastole. (Fig. 4.)

3. It is noteworthy that electrocardiographic signs of anoxemia as expressed by deviations of the S-T and T segments subside almost as soon as oxygen therapy is instituted. (See Figs. 2, 11, 15 and 16.)

FIG. 17. Represents the average of the fifteen patients. The average number of days of oxygen therapy at the time of the most significant change is 36. For the entire group of cases the change in pulse rate after oxygen therapy was instituted was from an average of 106 to 86. The average increase in the duration of the systolic period was small (from 0.341 to 0.339). This brought the ratio of systole to diastole to a more normal relationship (from 1.54 to 1.05).

line. At this phase the cardiac rate became slow and the diastolic period became significantly prolonged.

All patients showed unequivocal clinical improvement* as the electrical sequence of events approached a more normal relationship. It may be stated that in those instances in which the patient was removed from the oxygen room shortly after these apparent beneficial effects were attained, a reversal of the progress at once became manifest. The cardiac rate increased and the relationship of systole to diastole returned to the level observed before oxygen therapy was begun. In those instances in which oxygen therapy was prolonged for several weeks beyond the point of apparent improvement the benefits seemed to persist. Each patient in our present series seemed to require an individual period of oxygen therapy before the apparent beneficial effects became permanent. It is hoped that further experience with this form of therapy will bring to light criteria which might help in the decision as to how long oxygen therapy should be continued.

COMMENT

In our experience the sequence of events in the progress of cardiac disability in acute carditis in children usually follows a distinct electrocardiographic and clinical pattern. In the acute exudative phase, when the heart is acutely inflamed, the tumultuous cardiac action is expressed in a delay in the period of heart muscle contraction at the expense of the period of relaxation. The more severe the clinical carditis the longer the duration of contraction and the shorter the period of relaxation. When the period of relaxation becomes abnormally short, the patient begins to show some subjective signs of cardiac insufficiency, such as dyspnea on exertion, cardiac fatigue, etc. At this stage the electrocardiogram usually shows signs of anoxia. In cases in which the electrocardiographic evidence of anoxemia continues for a long period of time other evidence of progressive cardiac disability may become manifest. Some patients begin at this stage to develop various forms of disturbance in rhythm—premature contractions, paroxysmal auricular flutter, paroxysmal auricular fibrillation, etc. Other patients continue to develop further cardiac dilatation and hypertrophy and finally begin to show objective evidence of congestive heart failure.

Our observations would seem to show that the administration of oxygen during the early anoxic phase of acute carditis favorably influences the course of acute carditis. The mechanism by which oxygen therapy produces these apparent beneficial effects is not clear. If we are to assume that an increase in the oxygen saturation of the arterial blood may help to prevent or improve local tissue anoxia, inhalation of an oxygen-enriched atmosphere containing 45 per cent to 50 per cent oxygen would be expected to raise the oxygen saturation of the arterial blood in cardiac patients, restoring the oxygen tension and presumably in this way reversing the ill effects of anoxemia. Whether this mechanism may play a part in effecting improvement in the functional disability of the heart during the course of acute carditis is now under investigation.

The observations presented here show that oxygen therapy decreases cardiac overactivity and that the heart action approaches a more normal tempo even with persistence of acute carditis. This is apparently accomplished by restoring a more normal relationship in the duration of systole to that of diastole. This restoration may be effected by decreasing the duration of systole or by lengthening the duration of diastole. As shown elsewhere[1] systole occupies a relatively smaller portion of the cardiac cycle as carditis subsides and thus the relationship of systole to diastole becomes more normal. In oxygen therapy, however, the diastolic period becomes very much prolonged while the duration of

* The nature of clinical improvement has been described elsewhere.[3]

systole is only slightly altered. The restoration to a normal relationship is accomplished by the device of lengthening the diastolic period.

It is reasonable to postulate that an increase in the period of relaxation (perfusion time) might improve the chemical economy of the heart. And it is noteworthy that this mechanism is attained without disturbing measurably the delay in contraction which may be a compensatory response of the acutely inflamed heart muscle.

It obviously cannot be said from these observations that oxygen therapy significantly and rapidly influences the acute inflammatory process in the heart in acute carditis. On the other hand, it seems apparent that the functional disturbance of the heart action resulting from a shortening of the period of cardiac relaxation and a lengthening of the period of contraction is significantly improved even while the inflammatory process continues. The effect of this improvement upon total cardiac disability resulting from rheumatic carditis forms the subject of further investigation.

SUMMARY AND CONCLUSIONS

1. Fifteen representative cases of acute rheumatic carditis in children who showed definite clinical improvement with oxygen therapy are analyzed.

2. All patients showed a return of the Q-T:T-Q ratio in the direction of normal when oxygen therapy was instituted.

3. Restoration of a normal systolic: diastolic ratio was attained by prolongation of the diastolic period while the systolic period remained unchanged.

4. It is believed that improvement in the functional cardiac disability of acute carditis observed in oxygen therapy may prevent further cardiac damage during the acute phase of carditis.

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Review

The Treatment of Pneumococcal Meningitis*

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THE past decade has witnessed remarkable progress in the therapy of many of the common bacterial infections. Not among the least of the accomplishments of these years have been improvements in the management of purulent meningitis. With the emergence in rather rapid succession of antisera, sulfonamide derivatives and penicillin, it is appropriate to survey the results which have been obtained with these agents singly and together in situations in which they have proved partly or outstandingly effective. It is the purpose of this review to detail the experiences of this and other clinics in the therapy of infections of the meninges due to the pneumococcus. In examining reports of a large number of cases, opportunity was afforded to collect statistics on the course of the disease as modified by therapy. While little of this information is new, confirmation on the basis of a fairly large number of cases appears worth while.

As a cause of meningitis the pneumococcus is exceeded in frequency by the Mycobacterium tuberculosis and the meningococcus; it is usually stated to be slightly more common than the hemolytic streptococcus. In a series of approximately 5,000 subjects collected by Keefer,[1] the offending organism was M. tuberculosis in about 1,500 and meningococcus in 2,000 while the pneumococcus was isolated from slightly over 500 patients and the hemolytic streptococcus from about 400.

It is known that the pneumococcus may gain access to the meninges from adjacent foci of suppuration such as the middle ear, or by hematogenous extension from the lungs. Infection also commonly arises in the absence of demonstrable foci but sometimes enters through skull fracture, either traumatic or operative. Linell and Robinson[2] have reported cases of pneumococcal meningitis developing years after head injury. Organisms appeared to have entered through old fracture lines where bony union had failed to occur. Finland,[7] Toomey,[8] Rhoads[10] and Hartman[14] have described a number of patients with pneumococcal meningitis with a remote history of skull fracture or head injury.

Reference to Table 1 shows that in a total of 409 patients meningitis resulted from extension of infection in the ears or mastoid bones in 151, as a primary disease in 122, followed pneumonia in 101 and resulted from traumatic skull fracture in nineteen patients. Sinusitis occurred as the initial infection in thirteen subjects while meningitis resulted three times after cranial operation (brain tumor once, nasal cavity twice). It is of interest that while about 25 per cent of all cases appearing in the table arose from pre-existing pulmonary infection, the disease is actually an uncommon complication of pneumonia, the incidence according to Heffron[3] being between 0.4 and 1.9 per cent.

Invasion of the meninges by the pneumococcus occurs at all ages and the distribution in 249 patients is given in part B of Table 1. Children in the first decade appear to be attacked twice as often as any other group, over one-fourth of the total, according to recent reports occurring in the first two years of life. Undoubtedly this is an expres-

* From the Haynes Memorial and Evans Memorial, Mass. Memorial Hospitals and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

sion of the frequency of middle ear and mastoid disease in young children.

In 433 cases the serologic type of the offending pneumococcus was stated and these are shown in part D of Table 1 where it is seen that half of all cases were caused by the first eight types and another fourth by types 12, 14 and 18. It is of interest that types 4 and 6, which do not often cause lobar pneumonia, were isolated as often as those more commonly associated with pulmonary infection.

TABLE 1

PNEUMOCOCCAL MENINGITIS

A. Origin of Meningitis in 409 Cases

Site of Origin	No. of Cases
Middle ear and mastoid disease	151
Primary	122
Pneumonia	101
Skull fracture	19
Sinusitis	13
Cranial operation	3

B. Age Incidence in 249 Cases

Age	No. of Cases
0– 2	74
2–10	35
10–20	30
20–30	14
30–40	3
40–50	35
50–60	46
60	12

C. Blood Cultures in 201 Cases

Positive	117
Negative	84

D. Serologic Type of Pneumococcus in 433 Cases

Type	Per Cent	of Cases
1	7	
2	2	
3	13	
4	6	
5	7	
6	6	
7	6	
8	3	—
		50
12	6	
14	7	
18	9	—
		22
All others	28	

E. Mortality in Pneumococcal Meningitis Prior to the Use of the Sulfonamides

Clinic	Total Cases	No. of Recoveries
Charity Hospital, New Orleans[19]	111	1
Cleveland City[8]	157	0
Sydenham[9]	29	0
Children's, Washington[20]	50	0
Harriet Lane Home[39]	150	0
Children's, Boston[30]	35	0
Boston City Hospital[7]	99	0
Total	631	1

Consideration of clinical and laboratory diagnostic features of pneumococcal meningitis is beyond the scope of this review. However, in cases of intracranial disease following infection elsewhere in the body, certain conditions other than meningitis must be considered if the neurologic and spinal fluid findings are atypical. Reference is made to the important paper of Kubik and Adams[2a] who re-emphasize the syndrome of subdural empyema which is a neurosurgical emergency.

Before 1936 almost all cases of pneumococcal meningitis resulted fatally. Therapy was confined principally to surgical attack on infected foci and constant or intermittent drainage of the subarachnoid space. Several substances, including various dyes and (later) ethyl hydrocupreine, were employed as possible antibacterial agents. While the latter may have been of some value in certain local infections due to the pneumococcus, none of these drugs influenced the mortality in patients with meningitis. Specific antipneumococcus horse serum may have produced isolated recoveries but regularly successful therapy was delayed until the advent of the sulfonamide derivatives. Goldstein and Goldstein[4] in 1947 collected from world literature 150 reports of recoveries from what they believed to be pneumococcal meningitis. Vogelius,[12] however, re-examined the original reports, available in twenty-two instances, and was unwilling to accept the diagnosis in any of these. The outlook in the presulfonamide era is perhaps better depicted in part E of Table 1 in which 631 case reports have been collected. Of these there was only one recovery.

In 1936 a few patients with various infections were treated with azosulfamide and prontosil; shortly thereafter sulfanilamide became available to be followed within a

year by sulfapyridine. During this period more or less concentrated rabbit antiserum began to be marketed for use against an increasing number of common serologic types of pneumococcus. By the summer of 1937 reports of successfully treated pneumococcal meningitis began to appear and it soon became apparent that certain patients with this hitherto uniformly fatal infection could be cured. In 1941 Steele and Gottlieb[5] were able to collect data on 115 patients among whom there were sixty-nine recoveries. This review contains references to the earliest reported patients treated with sulfonamides. Fifty-seven of these patients were given sulfanilamide while sixty-eight were treated with sulfapyridine. No important difference was noted in the efficacy of the two drugs. The value of specific antiserum, also administered to twenty-six patients of the whole group, will be discussed later. Steele and Gottlieb anticipated the objection of later writers that the recovery rate of 60 per cent was too high. Their material contains numerous papers describing only two or three patients with 100 per cent survival, and such a compilation necessarily omits small groups of therapeutic failures which are less likely to be published. The same criticism applies to the earlier review of Coleman[6] who arrived at a recovery rate of 69 per cent in reports collected from British literature. In surveying publications subsequent to these papers it was decided to consider only those reports describing six or more patients in order to determine more accurately the true experience with sulfonamides. Smaller groups were accepted, however, when they were presented as parts of a series treated by more than one method. This was done in order to include early penicillin results published by authors reporting numerous sulfonamide-treated patients and appending accounts of penicillin in the limited number of patients for whom it was at first available.

No effort was made to eliminate patients who died very early after treatment was begun, nor were patients separated on the basis of which sulfonamide drugs were employed. No evaluation was made of various methods of spinal fluid drainage employed in some of the material examined, nor was account taken of the minority of subjects receiving intrathecal injection of solutions of sulfonamide.

Table II contains recovery rates from 196 well described reports of sulfonamide-treated patients which have appeared since 1940.* These values range between 0 and 40 per cent; the best results are less than the 60 per cent survivals estimated by Steele and Gottlieb. The average of 25 per cent is significantly lower for reasons already given. In Table III detailed analysis of 181 subjects is presented. Certain of the reports from Table II are omitted because data were incomplete or were not analyzed in the same manner as in Table III. The patients of Finland, Toomey and the first series of Hodes were included in the review of Steele and Gottlieb, but are introduced into Table III because they represent thirty-nine well described patients. Of interest is the fact that the gross recovery rate of this new group is 29 per cent, not differing significantly from the 25 per cent of Table II.

The series of Finland, with 60 per cent survivals, is the sole report which equals the rate calculated by Steele and Gottlieb. All authors in describing pneumococcal meningitis have remarked upon the variation in results encountered from one clinic to another, suggesting the possibility of "mild," "moderate" and "severe" cases. The non-existence of mild or moderate pneumococcal meningitis is documented in part E of Table I. It is, however, true that the response to therapy is significantly altered by certain factors, some of which may be identified in Table III. At once apparent is the influence of the patient's age. While fourteen of twenty-nine patients between two and ten

* Seventy-three patients with four recoveries reported by Dowling[16] and his colleagues are not included. These were collected from the files of various hospitals and some were neither treated nor seen by the authors. It is not believed that they represent the results which may be obtained with sulfonamides under the most favorable conditions. This paper, however, was a valuable addition to the material presented in Table I.

years were successfully treated with sulfonamides, only four of twenty-eight infants under two recovered. The outcome was favorable in nearly one-third of patients between thirty and fifty, whereas only about one-eighth past fifty were cured. The survival rate of only 20 per cent in the age group twenty to thirty is of doubtful significance since only eight patients in this decade were reported; and of this small number several were complicated, since there are included a pregnant female with pneumonia and two persons with head injury.

Steele and Gottlieb, as well as most of the clinicians who have described their cases subsequently, have expressed the view that prognosis is not greatly influenced by demonstration of pneumococcal bacteremia during meningitis. Ninety-five blood cultures were reported in the sulfonamide-treated patients and about half were positive. Of these, 32 per cent survived while, of those from whom the organism was not isolated, 45 per cent recovered. Thus, invasion of the blood stream alters the outlook only slightly if at all. Of great importance, on the other hand, was the source of meningeal infection. Disease of the middle ear or mastoid was the precursor of meningitis in over a third of the recorded

TABLE II
RECOVERY RATES IN COLLECTED CASES OF PNEUMOCOCCAL MENINGITIS TREATED WITH SULFONAMIDES

A. Patients Treated with Sulfonamides with or without Antiserum

Author	No. of Cases	Recoveries, Per Cent
Steele and Gottlieb[5] (collected cases)	115	60
Rhoads[10]	22	32
Neal	30	33
Vogelius[12]	18	22
Feldman[13]	6	0
Hartman[14]	26	35
Hodes (second series)	43	40
Sweet[15]	40	8
Weller[18]	11	0
Ross[35]	54	22
Total since Steele and Gottlieb	250	25

B. Patients Treated with Sulfonamides Alone

Author	No. of Cases	Recoveries, Per Cent
Steele and Gottlieb (collected cases)	89	57
Subsequent reported cases	98	27
Total	187	41

C. Patients Treated with Sulfonamides and Specific Antiserum

Author	No. of Cases	Recoveries, Per Cent
Steele and Gottlieb (collected cases)	26	69
Subsequent reported cases	140	35
Total	166	42

TABLE II—(*Continued*)

D. Patients under Age Two Years Treated with Sulfonamides with and without Specific Antiserum

	Cases	No. of Recoveries
Without serum	23	1
With serum	33	10

E. Comparison of Results with Sulfonamides and with Penicillin (with or without Sulfonamides) in Cases in Which the Prognosis Is Known to Be Poor

	Sulfonamides		Penicillin	
	No. of Cases	Recoveries, Per Cent	No. of Cases	Recoveries, Per Cent
Patients under age 2	28	14	58	69
Patients over age 50	15	13	67	34
Meningitis following pneumonia	40	13	41	47

Steele and Gottlieb, as well as most of the clinicians who have described their cases subsequently, have expressed the view that prognosis is not greatly influenced by demonstration of pneumococcal bacteremia during meningitis. Ninety-five blood cultures were reported in the sulfonamide-treated patients and about half were positive. Of these, 32 per cent survived while, of those from whom the organism was not isolated, 45 per cent recovered. Thus, invasion of the blood stream alters the outlook only slightly if at all. Of great importance, on the other hand, was the source of meningeal infection. Disease of the middle ear or mastoid was the precursor of meningitis in over a third of the recorded

instances and the incidence of recovery was 36 per cent. To avoid the introduction of an additional column into Table III, three patients with sinusitis with aural and mastoid infection are included. In a somewhat smaller number of patients no focus could be found and the survival rate was 31 per cent. However, when pneumonia was present, the prognosis was substantially altered for only 13 per cent were cured. The patients following skull fracture and operation on the cranial vault were too few in number to permit any conclusions. Plainly, the outlook in head injury is also greatly modified by such brain trauma as has occurred. Endocarditis was found postmortem ten times but was not suspected in any patient who recovered. One brain abscess was diagnosed and successfully drained and seven others were found at autopsy.

These factors explain, in part, some of the unusual therapeutic results recorded in the literature. In Finland's group with 60 per cent cures there were no infants, no patients over the age of fifty and only one with pneumonia. On the other hand, Feldman, who observed no recoveries, treated patients two-thirds of whom were over fifty and one-half of whom had pneumonia. The series of Sweet is unfavorably biased for the same reasons. Hence the alleged variation in the results obtained with the sulfonamides is more apparent than real and the recovery rate of about 30 per cent which is proposed in Tables II and III in all likelihood affords a reasonable estimate of what may be expected from these agents under ordinary circumstances.

Because of the great efficacy of newer drugs in the treatment of pneumococcal infections of all varieties, and also because

TABLE III

ANALYSIS OF 181 CASES OF PNEUMOCOCCAL MENINGITIS IN WHICH SULFONAMIDES WERE USED

Author	Totals	Age Group in Years							Blood Culture		Pathogenesis of Meningitis					Other Rx		Additional Lesions	
		0–2	2–10	10–20	20–30	30–40	40–50	50+	Pos.	Neg.	Sinus Ear*	Primary	Pneumonia	Post-operative	Skull Frac.	None	Serum	Endocarditis	Brain Abscess
Finland[7]	Cases 10	0	4	4	0	0	2	0	4	6	2	2	1	2	3	5	5	1	1
	Cures 6	0	3	3	0	0	0	0	0	6	1	1	0	1	3	3	3	0	0
	Per cent 60																		
Toomey[8]	Cases 12	2	0	2	2	3	1	2	3	0	3	2	5	1	1	6	6	2	0
	Cures 5	0	0	2	1	1	0	1	1	0	2	1	1	1	0	2	3	0	0
	Per cent 42																		
Hodes[9]	Cases 17	4	2	3	1	4	2	1	9	8	8	5	3	0	0	17	0	0	1
	Cures 8	0	1	2	0	3	2	0	4	4	4	3	1	0	0	8	0	0	0
	Per cent 47																		
Rhoads[10]	Cases 22	1	3	6	1	3	5	3	13	5	6	9	5	0	2	5	17	3	1
	Cures 7	0	1	4	0	0	1	1	5	2	2	4	1	0	0	0	7	0	0
	Per cent 32																		
Neal[11]	Cases 30	5	5	3	4	2	8	3	10	10	20	7	0	0	3	9	21	0	2
	Cures 10	1	3	2	0	0	4	0	4	4	6	3	0	0	1	3	7	0	1
	Per cent 33																		
Vogelius[12]	Cases 18	4	1	5	2	3	1	2	..	..	11	6	1	0	0	4	14	0	0
	Cures 4	0	0	3	1	0	0	0	..	..	2	2	0	0	0	1	3	0	0
	Per cent 22																		
Feldman[13]	Cases 6	0	1	0	0	0	1	4	3	3	1	2	3	0	0	3	3	0	0
	Cures 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Per cent 0																		
Hartman[14]	Cases 26	12	13	1	0	0	0	0	11	10	15*	3	7	1	0	14	12	0	3
	Cures 9	3	6	0	0	0	0	0	3	3	8	1	0	0	0	3	6	0	0
	Per cent 35																		
Sweet[15]	Cases 40	6			8			26	..	..	4	15	15	0	2	19	21	4	0
	Cures 3	1			0			2	..	..	0	1	2	0	0	?	?	0	0
	Per cent 8																		
Totals	Cases 181	28	29	24	10	15	20	15	53	42	70	51	40	4	11	63	78	10	8
	Cures 52	4	14	16	2	4	7	2	17	19	25	16	5	2	4	20	29	0	1
	Per cent 29	14	48	67	20	27	35	13	32	45	36	31	13	50	36	32	37	0	13

* Entries in this column refer to ear or mastoid infection except for three cases of sinusitis with one recovery reported by Hartman.

of the disappearance of commercial sources of type-specific antiserum, evaluation of antisera in the treatment of pneumococcal meningitis is no longer of practical concern. It is, however, a matter of historic interest and of some theoretic importance in the general therapy of bacterial disease. Certain clinical and experimental considerations in serotherapy of pneumococcal meningitis have been discussed by Finland.[7] Briefly, in bacteremia accompanying lobar pneumonia organisms were often observed to proliferate in the circulating blood despite ordinarily adequate sulfanilamide treatment and sterilization occurred only after the establishment of a sufficiency of type-specific antibody, occurring either spontaneously or as a result of administration of antiserum. The continued multiplication of pneumococci was also observed to occur in the spinal fluid of certain patients while sulfanilamide was being administered and it was again found that sterilization might occur promptly when an antibody balance was established. Neither complement nor antibody, however, could be demonstrated regularly in the spinal fluid even when present in large amounts in the blood. This, of course, argued for the injection of type-specific antiserum into the subarachnoid space. Numerous observers were aware, however, that patients became worse in a manner quite different from any foreign protein reaction after intrathecal injection of serum. On the basis of test tube experiment, Finland found that large amounts of antiserum produced large aggregates of organisms and that phagocytosis was impaired mechanically and possibly by toxic action of the specific precipitate produced by the antigen-antibody combination on the granulocytes. He postulated further that this relatively massive agglutination might lead to subarachnoid block. On the basis of all these considerations it was suggested that the ideal in serotherapy might be production of antibody excess in the blood, artificially if necessary, and injection of only a small amount of antiserum into the intrathecal space. In certain instances Finland injected the patient's own serum after it was demonstrated to be immune. This plan was used in some of his cases considered in Table III.

Table II contains information available regarding the value of serum as an adjuvant to sulfonamides. Steele and Gottlieb in their collected data found 57 per cent recoveries in patients treated by chemotherapy alone and 69 per cent in those who also received antiserum. They did not believe that this difference was significant. In subsequent reports (Table III) recovery rate without serum was 27 per cent, while on combined treatment 35 per cent survived. Adding these more recent results to those of Steele and Gottlieb the comparative rates are 41 and 42 per cent, respectively, and it seems clear that addition of antiserum was of no value. Quite different, however, was the conclusion of Hodes,[17] who found that of thirty-two infants under age two (not all of whom could be included in Table III), six of eighteen treated with both agents recovered, while there was only one survival of fourteen patients treated with sulfonamide alone. In part D of Table II the available experience of others who have reported results in infants is added to that of Hodes and it is seen that only one cure was found among twenty-three patients treated by chemotherapy alone. The combination of serum and sulfonamide, employed in thirty-three babies, produced ten recoveries. The surviving group is not large enough to be divided on the basis of intrathecal and exclusively parathecal serotherapy. It is unfortunate that the serum question could not be examined in those infants in whom meningitis followed pneumonia; of recoveries in this situation, only three detailed descriptions could be found. It must be concluded, therefore, that the value of type-specific antiserum in sulfonamide-treated pneumococcal meningitis was never definitely determined. In infants serum-sulfonamide combinations produced strikingly better results than sulfonamide alone in the reported cases.

Since so many cases of pneumococcal meningitis arise from cranial suppuration, especially of the middle ear and mastoid bones, many clinicians believed that surgical attack on accessible infected foci was indicated in addition to chemotherapy. Opinion as to the value of drainage, however, was divided. Neal was of the opinion that "the importance of the eradication by surgery of foci of infection cannot be overestimated," while Hodes and his colleagues advocated postponement of such procedures until marked improvement had occurred, waiting if necessary as long as two or three weeks. They stated that "This delay in surgical intervention . . . contributed to recovery in a number of our patients." This question was most difficult to examine statistically. Aural paracentesis was almost always carried out in the patients in Table III when otitis was thought to be present and there appeared to be no reason to condemn so simple a maneuver. Of the seventy patients with ear, mastoid or sinus disease sixteen were subjected to more complicated surgery (usually mastoidectomy) and nine recovered, a survival rate of 56 per cent. Of fifty-four patients not operated upon, 30 per cent lived. In the series of Neal the recovery after drainage of a patient with a brain abscess has already been mentioned. These figures are not offered as conclusive because the value of any generalization is highly doubtful in a situation in which so many variables operate in each case.

The rapidity of clinical and bacteriologic response to sulfonamide treatment was very variable. In those patients who recovered and who had had frequent lumbar punctures, the spinal fluid was usually sterile between the fourth and seventh days of therapy. In a few instances negative cultures were obtained earlier and occasional subjects were encountered in which bacteria were isolated for many days, but eventual recovery occurred. Clinical improvement usually preceded or followed disappearance of organisms from the spinal fluid by about two days.

Relapse was an event which occurred quite regularly with sulfonamide treatment of meningitis due to the pneumococcus. Coleman[6] found this accident six times among twenty-nine patients; at least ten other patients have been described, including several with multiple recurrences.[21–28] In the early days of sulfonamide chemotherapy it was common practice to reduce dosage of the drug as soon as a definite response occurred and this procedure was associated with most of the relapses which occurred before treatment had been discontinued. Renewed evidence of meningeal infection sometimes appeared as long as a month after cure had apparently been effected. Multiple recurrences were occasionally terminated by discovery and eradication of a previously unsuspected focus of infection; more often these searches were fruitless. In the material which appears in Table III, eight relapses were mentioned. This may not represent the true incidence since protocols were not always given in the fatal cases. Both of the patients observed by Neal and her group occurred about two weeks after apparently satisfactory therapy. One died; the other was successfully retreated. Hartman gives details of two patients who recovered after relapse associated with reduction in sulfonamide medication and one who was finally cured after an unexplained recurrence under full therapy. One of his cases relapsed after a month of observation and responded satisfactorily to re-treatment. Two patients showed transitory clinical and bacteriologic improvement and then died.

Complications following recovery from this disease have not been adequately described and information in regard to adults is especially deficient. Keefer[1] described arachnoiditis in his patient. In Finland's series deafness appeared early in one patient and was persistent. The patient whose disease followed partial removal of a brain tumor left the hospital with ataxia. Hodes mentioned slight weakness of one hand in a single patient. Hartman followed his group of infants and children especially carefully for the appearance of neurologic

residua. His studies included psychometric examinations and a number of serial encephalograms. He concluded that all young children during pneumococcal meningitis develop radiographically demonstrable hydrocephalus which may be transitory and without permanent effect. One of his patients, however, had persistence of this disorder associated with progressive mental deterioration. A second patient had convulsions and marked intellectual deficiency after two and one-half years. There were two children partly or totally deaf after more than six months and one with hemiparesis. Thus, severe and permanent neurologic damage occurred in five of Hartman's nine recoveries.

In summary, it may be said that recovery rate in pneumococcal meningitis treated with the sulfonamides is about 30 per cent and is influenced markedly by the patient's age and the source of the infection. The value of type-specific serotherapy as an adjuvant has never been properly assessed, but it appears to improve the results obtained in the treatment of infants. Also not evaluated, and possibly incapable of statistical evaluation, is surgical drainage of foci of infection which are commonly present. Relapse following sulfonamide therapy occurs regularly although not apparently with great frequency and is not necessarily associated with eventual fatality. Permanent neurologic damage has not been frequently reported in adults; in young children it is common and often severe.

In 1942 penicillin became available in small amounts and its value in the treatment of infections due to the pneumococcus soon became apparent. By August, 1943, the Committee on Chemotherapeutics of the National Research Council released a report describing the results obtained with the new drug in 500 subjects with various infections, including twenty-three patients with pneumococcal meningitis.[29] Only seven recoveries were noted, but the Committee remarked that the dosages were small and that not all of the patients had received intrathecal penicillin.

Table IV contains a partial analysis of 119 patients with pneumococcal meningitis treated with penicillin without the simultaneous administration of a sulfonamide. Most of these histories have also been collected by Walker and Johnson.[42] Only twenty-two of these patients could be analyzed in detail because of those reported by Appelbaum[32] and by White,[33] a total of twenty received simultaneous sulfonamide chemotherapy. These have been deducted from "totals," given in the first column of Table IV but could not be identified or removed from the analysis by age and focus of infection. These data are given in order to show the composition of the authors' groups, but they cannot be added to those known to have been treated without other agents. Eight reports of patients with sinusitis and ear and mastoid infections are tabulated.

Almost all of these patients had received sulfonamide in varying amounts prior to administration of penicillin. However, in over one-half of the group it was stated by the author that organisms were still present in the spinal fluid often in numbers large enough to permit direct typing. Two of the patients of Harford[31] were given courses of sulfonamide to diminish the likelihood of relapse after clinical and bacteriologic cure had been obtained with penicillin. Seven of the patients reported by White and his colleagues received no intrathecal penicillin and of these three recovered. The adults of White's group usually received between 50,000 and 100,000 units daily by intramuscular or intravenous injection. Two of Appelbaum's patients received exclusively intrathecal therapy.* With these exceptions, all other patients were treated with reasonable amounts of penicillin intramuscularly (or intravenously) and intrathecally. Most adults were given 20,000 to 30,000 units at least every three hours intramuscularly and from 10,000 to 20,000

* Cairns and his co-workers have reported four recoveries among eight patients in whom the only treatment consisted of introduction of penicillin into the cerebral ventricles or lumbar sac.[37]

units intrathecally once or twice daily. In addition to the intraspinal route injections were sometimes made into the basal cistern and occasionally into the ventricles. The doses of penicillin were limited by the early scarcity of the drug and often were not optimal by current standards. Moreover, the reported data are not ideal for purposes of analysis. Table IV represents, however, the available information on the efficacy of penicillin without simultaneous sulfonamide. Eleven of this group also received specific antiserum and it is known that of these six died. Thus, it is safe to state that mortality in the total group was not reduced by the use of serum.

Of the 119 patients fifty or 42 per cent survived. It should be noted that Table IV includes relatively more than twice as many patients under age two and past age fifty as does the sulfonamide series of Table III; the incidence of pneumonia, however, is nearly the same. Of ten infants treated with penicillin alone there were six recoveries. This number is too small to compare directly with the 14 per cent survival rate found with sulfonamides for this age group but suggests an improvement in results, as does the small series of patients over fifty.

TABLE IV

ANALYSIS OF CASES OF PNEUMOCOCCAL MENINGITIS IN WHICH PENICILLIN WITHOUT SULFONAMIDES WAS USED

Author	Totals	Age Group in Years							Blood Culture		Pathogenesis of Meningitis				Other Rx		Additional Lesions	
		0–2	2–10	10–20	20–30	30–40	40–50	50+	Pos.	Neg.	Sinus Ear*	Primary	Pneumonia	Skull Frac.	None	Serum	Endocarditis	Brain Abscess
Sweet[18]	Cases 3	0	0	0	0	0	1	2	..	..	1	1	1	0	3	0	0	0
	Cures 1	0	0	0	0	0	1	0	..	..	1	0	0	0	1	0	0	0
	Per cent 33																	
Hartman[14]	Cases 3	2	1	0	0	0	0	0	0	3	1	2	0	0	1	2	0	0
	Cures 1	1	0	0	0	0	0	0	0	1	1	0	0	0	1	0	0	0
	Per cent 33																	
Hutchins[20]	Cases 7	7	0	0	0	0	0	0	..	..	..	..	..	0	7	0	0	0
	Cures 5	5	0	0	0	0	0	0	..	..	..	..	..	0	5	0	0	0
	Per cent 72																	
Harford[21]	Cases 9	1	0	3	0	0	2	3	6	3	4	3	2	0	9	0	0	0
	Cures 8	0	0	3	0	0	2	3	6	2	4	3	1	0	8	0	0	0
	Per cent 89																	
Totals	Cases 22	10	1	3	0	0	3	5	6	6	6	6	3	0	20	2	0	0
	Cures 15	6	0	3	0	0	3	3	6	3	6	3	1	0	15	0	0	0
	Per cent 68	60	0	100	0	0	100	60	100	50	100	50	33	0	75	0	0	0
		(0–1)	(1–10)															
Appelbaum[22]	Cases 54	11	6	2	1	7	12	28	33	16	32*	16	17	2	50	4	0	2
	Cures 20	4	5	1	1	4	3	8	?	?	15	4	5	2	?	?	0	0
	Per cent 37																	
		(0–2)	(2–15)	(16–30)		(31–50)												
White[22]	Cases 43	12	9	6		12		17	23	18	29*	12	9	..	40	3	4	3
	Cures 15	5	4	0		7		2	8	8	8	6	4	..	14	1	0	0
	Per cent 34																	
Totals	Cases 119																	
	Cures 50																	
	Per cent 42																	

* Entries in this column refer to ear or mastoid infection except for eight cases of sinusitis. Of these two with no recoveries were reported by Appelbaum and six with one recovery by White.

In Table V appears an analysis of the reported patients treated simultaneously with penicillin and a sulfonamide and appended are the twenty subjects of White and of Appelbaum previously referred to. The overall recovery rate was 62 per cent which is twice that found with sulfonamide alone. In the sixty-six detailed reports it may be seen that there are few aged patients compared to those in the group treated by other methods. This is more than outweighed by the fact that of the sixty-six penicillin-sulfonamide treated patients, almost half were infants under age two and that 81 per cent recoveries were obtained

in this age group in which the outlook has always been so poor. An insufficient number of patients with meningitis consequent on pneumonia were treated by this plan to make any comparison.

An effort was made to present separately the results obtained with penicillin alone and those observed with adjuvant sulfonamide. Analysis suggests but does not prove that combined therapy is of greater value. It is unfortunate that of the cases treated with both agents, half of those suitable for detailed analysis also received type-specific antiserum. The results with and without this third drug were the same but comparison is further complicated.

In order to show clearly the great value of penicillin in meningitis due to the pneumococcus, the final section of Table II shows the results reported separately in infants, in the aged, in patients with pneumonia treated with sulfonamide and in those treated with penicillin, with or without sulfonamide. The results in patients who received penicillin are five times better in infants, over twice as good in the elderly and three and one-half times better in patients with pneumonia.

Results obtained in the treatment of pneumococcus meningitis at the Evans and Haynes Memorials are shown in Table VI. When penicillin became available, nine patients were treated with this agent alone and only one recovered. In view of the results obtained subsequently with combined therapy, an impression was formed as to the advantages of simultaneous sulfonamide administration which, in retrospect, is probably not justifiable. Examination of the discouraging cases in part A of Table VI shows that six of the nine patients were either infants or aged (three in fact were past sixty-five), and a formidable group of complications was encountered

TABLE V

ANALYSIS OF CASES OF PNEUMOCOCCAL MENINGITIS IN WHICH PENICILLIN AND SULFONAMIDE WERE USED

Author	Totals	Age Group in Years							Blood Culture		Pathogenesis of Meningitis				Other Rx		Additional Lesions	
		0–2	2–10	10–20	20–30	30–40	40–50	50+	Pos.	Neg.	Ear	Primary	Pneumonia	Skull Frac.	None	Serum	Endocarditis	Brain Abscess
A. J. Waring[21]	Cases 12	8	1	0	0	0	1	2	7	0	6	1	3	0	9	3	0	0
	Cures 11	7	1	0	0	0	1	2	?	0	6	1	3	0	8	3	0	0
	Per cent 92																	
Sweet[18]	Cases 13	2	0	1	1	1	6	2	..	..	1	7	3	1	11	2	1	0
	Cures 6	2	0	1	1	1	1	0	..	..	1	3	1	1	4	2	0	0
	Per cent 96																	
Hartman[14]	Cases 5	5	0	0	0	0	0	0	2	2	4	1	0	0	2	3	0	0
	Cures 3	3	0	0	0	0	0	0	2	1	3	0	0	0	1	2	0	0
	Per cent 60																	
Hutchins[20]	Cases 7	7	0	0	0	0	0	0	..	..	..	..	..	..	3	4	0	0
	Cures 4	4	0	0	0	0	0	0	..	..	..	..	..	..	2	2	0	0
	Per cent 57																	
Ross[25]	Cases 19	14	4	1	0	0	0	0	..	..	..	..	..	0	12	7	0	0
	Cures 16	13	3	0	0	0	0	0	..	..	..	..	..	0	10	6	0	0
	Per cent 84																	
Jepson[10]	Cases 10	All in Military Age Group							..	..	0	0	0	10	10	0	0	0
	Cures 5								..	..	0	0	0	5	5	0	0	0
	Per cent 50																	
Totals	Cases 66	36	5	2	1	1	7	4	2	2	11	9	6	11	47	19	1	0
	Cures 45	29	4	1	1	1	2	2	2	1	10	4	4	6	30	15	0	0
	Per cent 64	81	80	50	100	100	28	50	100	50	91	45	67	55	64	79	0	0
Appelbaum[22]	Cases 13																	
	Cures 5																	
	Per cent 38																	
White[23]	Cases 7																	
	Cures 3																	
	Per cent 43																	
Total	Cases 86																	
	Cures 53																	
	Per cent 62																	

including a brain abscess and a case of ulcerative endocarditis. One of the two patients in the less unfavorable age group had a major congenital heart lesion with marked cyanosis (without postmortem evidence of endocarditis). Of eighteen patients of their patients organisms could not be recovered twelve to twenty-four hours after treatment was begun. The fluid in fifty-three of Appelbaum's sixty-seven patients was sterile after forty-eight hours[32] and Hartman[14] obtained negative cultures from

TABLE VI

ANALYSIS OF EVANS AND HAYNES MEMORIAL CASES OF PNEUMOCOCCAL MENINGITIS IN WHICH PENICILLIN WAS USED

	Totals	Age Group, Years							Blood Culture		Pathogenesis of Meningitis					Other Rx		Additional Lesions
		0–2	2–10	10–20	20–30	30–40	40–50	50+	Pos.	Neg.	Ear	Sinus	Primary	Pneumonia	Skull Frac.	None	Serum	
A.	Cases 9	1	0	1	0	1	1	5	9	0	2	2	3	2	0	9	0	Brain abscess 1
	Cures 1	0	0	0	0	0	0	1	1	0	0	0	1	0	0	1	0	Pericarditis 1
	Per cent 11																	Congenital heart 1
																		Vascular accident 1
																		Endocarditis 1
B.	Cases 18	0	1	3	2	3	2	7	9	9	3	4	6	4	1	17	1	Endocarditis ?2
	Cures 15	0	1	3	2	2	1	6	7	8	2	3	6	3	1	15	0	Previous recovery 1
	Per cent 83																	Diabetes 1

A. Patients treated with penicillin without simultaneous sulfonamide.
B. Patients treated with penicillin and sulfonamide.

treated with both penicillin and sulfonamide, there were fifteen recoveries (78 per cent). Although there were no infants in this series, seven of the group were over fifty years old and three of the four patients with pneumonia were in the sixth decade of life. Hence, it is not believed that this material is unduly biased by favorable statistical selection. However, these results are neither suitable for comparison with those reported in the treatment of infants nor should they be compared strictly with those obtained in this clinic with penicillin alone. This latter reservation may possibly apply also to the report of Smith and his colleagues[38] who obtained 63 per cent recoveries without the use of sulfonamide and 90 per cent with combined treatment. Their paper described nineteen cases in each group but did not present the details of individual patients.

In general, sterilization of the spinal fluid appeared to occur more promptly in penicillin-treated patients than in those of the sulfonamide series. Waring and Smith[34] gave four days as the average time in their cases and they found that in over one-half most of his patients on the second day. Relapse, however, was encountered regularly and was definitely mentioned eighteen times in the collected cases, which suggests that this difficulty was at least as frequent with penicillin as with sulfonamide. It was seen in one of the twenty-seven patients at this clinic but recovery ensued after three recurrences all during treatment. More often, however, relapses developed soon after therapy was discontinued. Neurologic complications appearing during or after treatment of pneumococcal meningitis are of especial interest and importance since some clinicians believe that certain of these changes result from the subarachnoid injection of penicillin rather than from the disease itself. This possibility is discussed in a subsequent section.

A two month old infant treated by Waring and Smith[34] made a prompt bacteriologic and clinical response but developed optic atrophy and blindness. This patient received an intrathecal injection of 20,000 units of penicillin. In view of this dose, relatively large for an infant, and the otherwise favorable course of the infection, it was

suggested that the medication rather than the meningitis may have caused this complication. Sweet and his colleagues[15] encountered two mild and two severe cases of myelopathy about whom they raised this question.

Aside from their case of blindness Waring and Smith reported one patient who became deaf and one with spastic monoplegia. In White's series[33] three young children were spastic but were said to be improving. One patient whose age was not given developed a "mental disturbance" and died three and one-half months after his meningitis was healed. Ross[35] encountered a case of deafness and one of spasticity and blindness. Hutchins[30] reported persistent hydrocephalus once, "motor retardation" once and four patients with severe cerebral damage, one of whom died two months later presumably of this cause. One example of hemiparesis, one of deafness and one of severe hydrocephalus were described by Hartman.[14] Two of the fatalities in his series were shown to have made a bacteriologic recovery but died during or shortly after treatment, probably from brain damage. Thus of 103 patients who survived therapy consisting wholly or in part of penicillin, significant central nervous system residuals were mentioned in twenty-three.

Brain abscess was present in five of the published cases and was found once among the group of the Evans and Haynes Memorials. None of these patients survived. There was autopsy proof or convincing clinical evidence of ulcerative endocarditis in six of the cases here reviewed and in three of the observed series. Since no report of recovery from pneumococcus meningitis complicated by endocarditis has been encountered, 2 patients in whom this combination appeared probable are briefly described. Both were treated with penicillin and sulfonamide.

CASE REPORTS

CASE I. A forty-nine year old man developed pneumococcus meningitis while supposedly convalescing from his third attack of pneumonia in six months. Bacteremia was demonstrated. He responded well to treatment but in the third week in the hospital a loud aortic diastolic murmur was heard for the first time. Congestive failure developed rapidly and was controlled only intermittently by digitalis. He died of cardiac decompensation thirteen months later. Permission for autopsy was denied.

CASE II. A thirty-eight year old woman, believed to be an alcoholic, developed pneumococcus meningitis with bacteremia after a prolonged respiratory infection of uncertain type. An aortic diastolic murmur was first discovered the day following admission. Infection was promptly controlled and no cardiac symptoms appeared although tachycardia and a gallop rhythm were repeatedly found and digitalis was given. Two months later she had no complaints and was then lost from observation. She died of pneumonia in another hospital after about six months and it was stated that a clean perforation was found in one of the aortic cusps at postmortem.

An unusual patient in the Haynes material was a young male who recovered from meningitis due to pneumococcus type 24. Six years before he had sustained a head injury and had been successfully treated with sulfanilamide and sulfapyridine for pneumococcus meningitis, type 6. This patient is most interesting in light of the observations of Linell and Robinson,[2] already mentioned.

Briefly, it may be concluded that penicillin has significantly improved the recovery rate in pneumococcal meningitis. Statistical proof of the efficacy of penicillin rests especially upon results obtained in young children and is most striking when adjuvant sulfonamide chemotherapy is used. The overall value of this combined therapy cannot be rigidly determined but the gross recovery rate appears to be somewhat higher (Tables IV and V) when both agents are used. Serious prolonged or permanent neurologic complications were described in about 20 per cent of the penicillin-treated cases. The spinal fluid is usually sterilized more promptly with penicillin than with sulfonamides. Tendency to relapse appears to be about the same as with

the latter agent. On the basis of the information available it is not possible to estimate the value of surgical treatment of demonstrable foci of infection in penicillin-treated cases.

As experience with penicillin treatment of bacterial meningitis has accumulated several authors have suggested that introduction of this agent directly into the subarachnoid system is unnecessary, and others urge that under certain circumstances it may even be dangerous.

It is generally accepted that in normal persons penicillin does not appear in the spinal fluid in significant amounts after intravenous or intramuscular injection of ordinary or even large doses.[39,46] While Rosenberg and Sylvester[40] have shown that therapeutic levels are present in the spinal fluids of patients with meningitis up to 140 minutes after parathecal administration, the studies of Ross[35] and of Cooke and Goldring[41] clearly show that effective amounts of penicillin do not cross the blood brain barrier in all or even in the majority of cases despite the presence of meningeal inflammation. Walker and Johnson[42] agree that systemic injections cannot be depended upon to produce optimal levels in the cerebrospinal fluid. However, because intrathecal penicillin is occasionally followed by nervous system damage, the whole concept of topical therapy to the meninges has been questioned on the ground that the antibacterial agent in the circulating blood may be adequate to sterilize these tissues without re-enforcement from the spinal fluid. While this possibility cannot be denied, it has not been established in pneumococcal meningitis by reports of isolated cures obtained exclusively by systemic therapy.[29,33,43] Since penicillin is known to be highly effective against the pneumococcus, it is not surprising that a certain number of recoveries occur with treatment programs of less than maximal intensity. However, it was pointed out earlier in this discussion that the reported overall mortality of patients with penicillin-treated pneumococcal meningitis is still 40 per cent; thus, any reduction in therapeutic effort based only on theoretic reasoning seems unjustified.

A more difficult problem is posed by observations which suggest that introduction of penicillin directly into the nervous system is not a safe procedure under all conditions. Headache and pleocytosis in the spinal fluid were encountered in the early pharmacologic studies[39] of the drug but it has never been shown that these changes are important. Of interest but of uncertain significance is the simultaneous appearance of urticaria and the neurologic findings of peripheral neuritis in a patient under therapy for a joint space infection who received no intrathecal penicillin.[44] The more alarming manifestations associated with subarachnoid administration of this agent are of two types: (1) cortical irritation resulting in convulsions and (2) hypertrophy of the leptomeninges, sometimes causing radiculopathy and myelopathy.

Johnson and Walker[42] discussed the case of a baby in whom meningitis developed after a catheter was introduced into a cerebral ventricle to effect decompression. The infection was almost symptomless but when 50,000 units of penicillin in 5 cc. of normal saline were injected into the catheter, circulatory collapse and severe convulsions occurred which, however, were followed by spectacular improvement within a few hours. Milder seizures followed doses of 15,000 units in this patient and his infection was eventually cured. These investigators were able to produce fits regularly in cats and monkeys by superficial injections into the cortex and found the effect to be proportional to the amount of penicillin introduced and to occur with highly purified or crystalline preparations. When deactivation of the drug was accomplished by physical and chemical manipulations, the decrease in antibacterial potency was found to be fairly closely correlated with diminished irritative activity. Pilcher, Meacham and Smith[45] produced convulsions in dogs by cortical injections and also by cisternal and ventricular administration.

They emphasized that the convulsant dose for a 10 Kg. dog by the cisternal route is equivalent to over 50,000 units for a 70 Kg. human and interpreted their findings to mean only that excessive medication should be avoided.

Seizures in humans due to spinal or cisternal injection of penicillin have not been frequently observed but there are additional reports describing such episodes in patients who received excessive doses[46,47] although large amounts have been tolerated in other cases.[37] It is possible that overmedication accounted for persistent lateralized twitchings in a young infant treated with intrathecal penicillin for meningococcal meningitis at the Haynes Memorial although these episodes (as did some of those reported) occurred before the disease was fully controlled. Experimental and clinical evidence clearly shows that convulsions result when high penicillin levels are produced in the excitable areas of the nervous system, a situation which can be avoided when less massive doses are employed and injections are made only into the lumbar sac or basal cistern. The view that penicillin produces inflammation of the leptomeninges beyond that resulting from the infection is more difficult to assess. Reference has already been made to the appearance of symptoms of cord and root disorder in several patients treated with intrathecal injection. Walker[48] and Walker and Johnson[42] have described three additional cases and three other reports of single cases have appeared, one of these a patient with meningococcal meningitis.[49–51] Two patients were subjected to exploratory laminectomy and marked proliferation of the arachnoid was found.[48,49] Experimentally injected normal monkeys were said to behave as if experiencing caudal paresthesia and to show at autopsy the previously described meningeal changes.[42]

Among patients treated at the Evans and Haynes Memorials complaints of root pain have been encountered with great frequency and occurred at the time injection was actually being made, disappearing within a few minutes. With the exception of one patient with foot drop, no persistent or permanent neurological residuals of root type have been seen and disability in this patient was believed at the time to have resulted from accidental injection of the sciatic nerve during simultaneous intramuscular administration.

On the basis of existing information it is not possible to separate clearly certain lesions possibly caused by therapy from those due to the violent leptomeningitis known to be produced by the pneumococcus. Some of the evidence incriminating penicillin as a cause of root and cord damage is quite suggestive and for the time being it seems necessary to view the development of such reactions as a possible hazard of intrathecal treatment; since excessive doses were not employed in all the recorded cases, it is one which is not readily preventable. Nevertheless, it is believed in this clinic that the risk of such an accident is preferable to any compromise in antibacterial therapy and it is, therefore, present practice to administer intrathecal penicillin to adults in amounts between 25,000 and 50,000 units and in volumes of at least 10 cc. of normal saline or spinal fluid. For infants and children the dose is reduced approximately in proportion to weight. The first two or three injections are sometimes given at twelve-hour intervals; otherwise they are made once daily. Walker and Johnson concluded, on the basis of their own and observations of others, that there is marked individual variation in the persistence of desirable spinal fluid levels after introduction of penicillin into either the spinal or cisternal spaces[42] and treatments at twelve-hour intervals may be indicated for several days in some cases. No sites of subarachnoid injection other than the lumbar sac and, on occasion, the basal cistern are employed. While cisternal treatment has not been routinely practiced, there is evidence that much better diffusion of penicillin into the cerebral ventricles occurs after cisternal than after lumbar administration.[42] Treat-

ment is usually continued for a minimum of ten days and is prolonged without hesitation if indications arise.

SUMMARY AND CONCLUSIONS

1. A number of features of the natural history of pneumococcus meningitis have been discussed. Prominent among these are the facts that about 40 per cent of cases arise from infection of the middle ear and about 25 per cent from pneumonia. The disease is common in infants and also occurs in the aged. Previous to the introduction of the sulfonamides almost all cases resulted fatally.

2. With appropriate treatment a substantial number of patients can be saved. The results in infants, the aged and in cases following pneumonia are distinctly less favorable, and it is of greatest importance to apply these facts in comparing the results of various clinics and of different therapeutic programs. With these limitations in mind, it is suggested that 30 per cent is a reasonable estimate of the recovery rate which may be expected from sulfonamide treatment. Similarly, 60 to 70 per cent is proposed for the penicillin survival rate, this figure including those patients who receive sulfonamides in addition. In adult patients treated early in the course of the disease it is possible that even better results may be obtained.

3. Penicillin is without question the agent of choice in the management of this disease. Systemic and topical administration is recommended. While there is suggestive evidence that subarachnoid injection of this drug may cause occasional reaction, untoward effects are not common if excessive dosage is avoided and the theoretic advantage of maintaining effective penicillin levels in the spinal fluid is great. This cannot be accomplished with certainty by exclusively systemic therapy. Simultaneous administration of sulfonamide is advised although rigid statistical proof of added effect is not available.

4. Neural complications are rather common especially in infants. Brain abscess and endocarditis are not common, but when present greatly reduce the chance of survival, although two patients recovered in this clinic despite probable endocarditis. These cases are briefly described.

5. An outline of the specific therapeutic principles employed at the Evans and Haynes Memorials follows:

(1) Establishment of bacteriologic diagnosis as rapidly as possible.

(2) Intramuscular penicillin, 40,000 units every three hours.

(3) Intrathecal penicillin injected into the lumbar sac in an amount not greater than 50,000 units for adults in a volume of at least 5 cc. of normal saline or spinal fluid. In patients weighing under 90 pounds dosage is reduced approximately by a factor equal to the weight divided by 100. In seriously ill patients the first two or three treatments are given at intervals of twelve hours, thereafter every twenty-four hours. If block is suspected or if free flow of fluid from the lumbar space becomes unobtainable, cisternal injections are made.

(4) Adequate hydration is urged. This may be accomplished by whatever means are necessary, as judged by the formation of moderately dilute urine during the first few hours in the hospital. Hydration should be followed by administration of sulfadiazine in amounts sufficient to produce a blood concentration of about 15 mg. per cent free drug. This has seemed to be easier with sulfadiazine than other compounds of the sulfonamide group. The urine is examined daily or more often.

(5) Necessary mechanical expedients to accomplish these ends in combative or comatose patients are physical restraint with soft flannel bandages, paraldehyde sedation freely but only when necessary and the use of the retention catheter.

6. Full therapy is usually continued for eight to ten days after the spinal fluid is sterile. If there is bacteriologic or other laboratory and clinical evidence of recovery of all known sites of infection, intrathecal penicillin is omitted. If progress is favorable, intramuscular penicillin is elimi-

nated during the next two or three days and sulfadiazine stopped before the end of that week.

5. The problem of surgical attack on infected foci has not been frequently encountered. It is tentatively believed that such intervention should be delayed until marked improvement has occurred or demonstrated to be highly unlikely as the result of antibiotic therapy.

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Seminars on Protein Hydrolysates

Utilization of Protein Hydrolysates by Normal and Protein-Depleted Animals*

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AMINO acids, arranged in various patterns into proteins, form the matrix of the living system; they are the catalysts, the centers around which the dynamic equilibria of life develop. Growth, maintenance and the well being of the living system are functions of the reproduction of these patterns, the formation of which are dependent upon a proper distribution and utilization of raw materials in the diet. The most fundamental of these raw materials are the so-called essential amino acids. They are the amino acids which cannot be manufactured by the animal body in sufficient quantities to meet its demands and must, therefore, be supplied in the diet.

Modern research on the nutritive rôle of amino acids began when mixtures of purified amino acids replaced proteins in the diet of animals, research which was inaugurated by Rose[1] at the University of Illinois in 1930. From these studies it was discovered that a mixture of ten of the amino acids, namely, valine, methionine, threonine, leucine, isoleucine, phenylalanine, tryptophane, lysine, histidine and arginine are essential for the growth of the rat. Recently Rose[2] has demonstrated that except for histidine and arginine these same amino acids are essential for the maintenance of nitrogen equilibrium in man.

NITROGEN EQUILIBRIUM

A study involving the measurement of nitrogen equilibrium is one of the most simple approaches to evaluation of amino acids or their derivatives in the living system. An animal is said to be in nitrogen equilibrium when the nitrogen intake is equal to the nitrogen excreted, a condition in which the nitrogen integrity of the animal is just being maintained. If one of the essential amino acids is eliminated from the diet, the animal cannot be maintained in nitrogen equilibrium but will excrete more nitrogen than is taken into the body. There are no body reserves of essential amino acids which can be drawn upon to supplement an inadequate pattern of dietary amino acids. The amount of dietary nitrogen necessary to maintain equilibrium increases, therefore, as the concentration of essential amino acids in the foodstuff decreases, becoming infinite if an essential amino acid is entirely absent. An acid hydrolysate of casein in which the tryptophane was destroyed by the acid would not, for example, maintain nitrogen equilibrium in a dog. When an optimum amount of this essential amino acid was added to the hydrolysate, the dog was maintained in nitrogen equilibrium by intravenous feedings of 300 mg. of nitrogen /day /Kg. of body weight. When insufficient tryptophane was

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added, 700 mg./day/Kg. of this same hydrolysate was fed intravenously to maintain nitrogen equilibrium. The minimum amount of nitrogen necessary to maintain nitrogen equilibrium is used, therefore, as a method of evaluating amino acids, protein

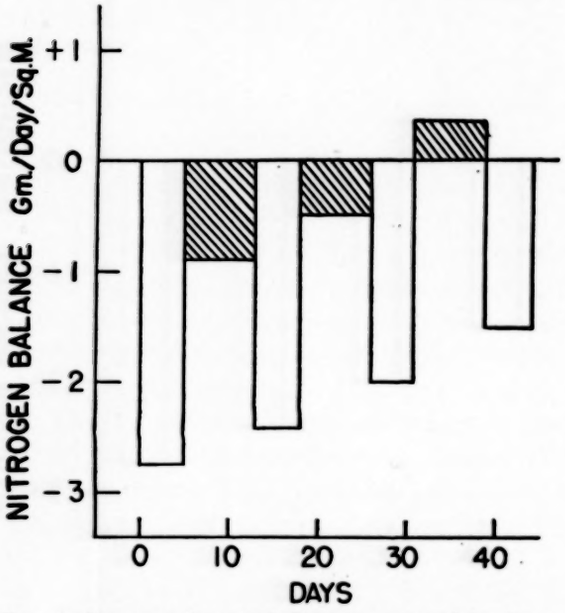

FIG. 1. Average nitrogen balances produced in three dogs fed a protein-free diet (white bars) and a diet containing a 3.60 Gm. wheat gluten nitrogen/day/sq. M. body surface area (bars with slanted lines).

hydrolysates and proteins in animals and in man. The objection to this method of evaluation is the variation in minima which is associated with changing protein stores.

The protein stores of the animal are the labile cytoplasmic proteins found in the liver, plasma and muscle tissues of the body. There are no protein reserves in the same sense that there are fat or carbohydrate reserves but the body can and does utilize cellular proteins to maintain the nitrogen integrity of essential tissues. When an animal is fed a protein-free diet, nitrogen is excreted in the urine, nitrogen which comes from the catabolism of tissue proteins. The amount of nitrogen excreted when the animal is eating a protein-free diet is a measure of the magnitude of the protein stores of the body, being high when the labile cytoplasmic proteins are in abundance and being low when these stores are depleted. Much less dietary nitrogen is needed to maintain the *status quo* of tissues in a protein-depleted animal than in one in which the tissues have grown in nitrogen to the fullest extent.

The relationship between nitrogen excretion and the protein stores of the animal are illustrated in Figure 1 in which the nitrogen balance is plotted against time in days. These are average data obtained on three dogs which were fed a protein-free diet for the first five days during which time they excreted 2.75 Gm. of nitrogen/day/sq. M. of body surface area (first white bar). Then the dogs received a constant protein intake of wheat gluten for eight days. During this period the nitrogen excretion was greater than the intake giving a negative nitrogen balance of 0.9 Gm./day/sq. M. (bar with slanted lines). The protein-free diet was substituted for wheat gluten for the next five days and the nitrogen excretion became 2.25 Gm./day/sq. M. In this way the dogs were fed alternately protein-free and the wheat gluten diet. The continued loss of tissue nitrogen while in negative nitrogen balance caused a gradual decrease in excretion of nitrogen so that after thirty days the wheat gluten diet was sufficient to put the dogs in positive nitrogen balance. Thus, the dogs went from a condition in which they lost nitrogen to one in which they gained nitrogen during the period of feeding of a constant quantity of protein. At the end of thirty days the dogs were so depleted in protein stores that much less dietary nitrogen was needed to maintain nitrogen equilibrium than at the beginning of the experiment.

Further effects of reducing the protein stores on nitrogen balance are illustrated in Figure 2. The data plotted in this figure illustrate results obtained while feeding a good source of nitrogen, such as egg proteins. This figure demonstrates that the relationship between absorbed nitrogen and nitrogen balance is linear in the region of negative nitrogen balance, the linearity extending over into positive balance be-

coming eventually curvilinear in this region. The linear relationship is defined by the following equation: NB = K (AN) − NEo when NB is nitrogen balance, K is the slope of the line, (AN) is absorbed nitrogen and NEo is the excretion of nitrogen on a protein-free diet, the Y intercept of the line.[3] As the excretion of body nitrogen decreases the amount of nitrogen necessary to maintain nitrogen equilibrium decreases. When the excretion of nitrogen on a protein-free diet (NEo), for example, is 3 Gm./day/sq. M., approximately 3.2 Gm./day/sq. M. of absorbed nitrogen are necessary to maintain nitrogen equilibrium, but when it is 1.3 Gm./day/sq. M. only 1.1 Gm./day/sq. M. are required.

Nitrogen Balance Indexes in Oral Feeding. The slope (K) of the lines in Figure 2 represent the rate of change of nitrogen balance with respect to absorbed nitrogen which is the rate at which a nitrogen source will establish equilibrium in an animal. For that reason this slope has been called the nitrogen balance index of the protein source.[4] Curve A represents data obtained on a normal dog while B illustrates the relationship found in a depleted animal. The nitrogen balance index is constant and independent of the protein stores in the normal dog but becomes a variable increasing in magnitude in the protein-depleted animal. The average index of the sample of egg protein illustrated by the data in this figure is 0.9 in normal dogs and is 1.0 in the depleted dog. The difference between the index in the normal and depleted animal becomes greater as the index decreases in value. The index for wheat gluten, for example, in the normal dog is 0.45 while in the depleted animal it is 0.7. The pattern of amino acids is retained better in the depleted than in the normal dog.[5]

As the protein stores decrease, reflected by a decrease in excretion of nitrogen on the protein-free diet (NEo), the curves extend further and further into the region of positive nitrogen balance. Thus, the possibilities for growth in nitrogen become greater and greater as the animal is depleted in proteins. Indeed, the degree of depletion can be estimated by the magnitude of positive nitrogen balance which can be produced in the animal.

Some nitrogen balance indexes obtained by oral feeding of various nitrogen sources to normal dogs are recorded in Table 1. The indexes vary from over unity for the best nitrogen sources to 0.4 for the poorest. More nitrogen is required, therefore, to maintain nitrogen equilibrium with wheat

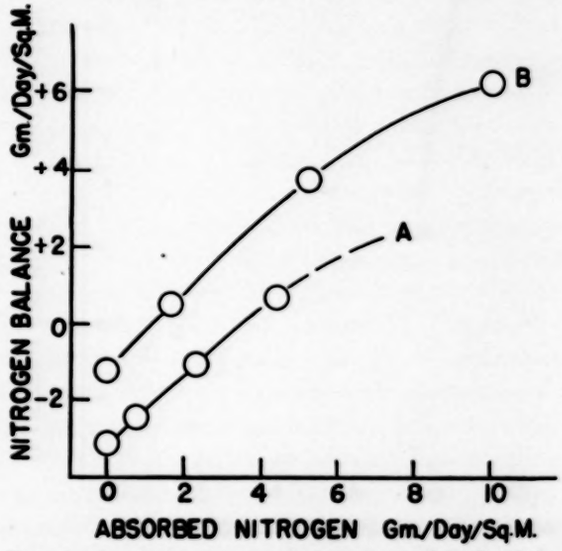

FIG. 2. Average nitrogen balances produced while feeding different amounts of whole egg nitrogen to three normal dogs (A) and three protein-depleted dogs (B). The data are expressed as Gm./day/sq. M of body surface area.

TABLE 1*

NITROGEN SOURCES AND NITROGEN BALANCE INDEXES IN NORMAL DOGS

Nitrogen Source	Nitrogen Balance Index K
Casein + methionine	1.2
Egg white	1.0
Lactalbumin	1.0
Lactalbumin hydrolysate	1.0
Bovine muscle meat	0.85
Casein	0.80
Casein hydrolysate	0.80
Wheat gluten + lysine	0.82
Chicken entrails	0.77
Flounder heads	0.55
Wheat gluten	0.44
α Protein	0.39

* Some of these data were taken from a paper by Allison, Anderson and Seeley.[4]

gluten than with egg white or whole egg proteins. The increase in the index of wheat gluten from 0.44 to 0.82 when lysine is added reflects an improvement in the amino acid pattern.[6] Similarly, casein is improved by adding methionine. Both the dog[7] and the rat[8,9] tend to be short on methionine so that addition of an optimum quantity of this amino acid to their diets often improves the retention of nitrogen in the animal, increasing in particular the liver stores of the animal.[10,11] This optimum quantity of methionine varies with the magnitude of the sulfur stores and a large excess of the amino acid over that needed to fill these stores will even reduce the retention of nitrogen. Thus, addition of methionine to the diet may increase or decrease the retention of nitrogen, depending upon the state of the sulfur stores of the animal and on the quantity of amino acid added. Cox et al.,[12] Johnson and coworkers[13] and Schwimmer et al.[14] found that the addition of methionine to the diet of man did not increase the retention of nitrogen which can be interpreted to mean that the addition of methionine provided an excess above the demands of normal metabolic processes.

When a mixture of amino acids is presented to the internal environment of the animal, the amino acids become a part of the dynamic equilibrium which characterizes the living system. Thus, the need for external supplementation will depend upon the components of that equilibrium. Mitchell[15] found, for example, that adding lysine to wheat gluten did not improve the retention of nitrogen in the adult rat. He suggested that the adult rat could synthesize lysine rapidly enough to take care of the needs for maintenance but that the young and growing rat could not. Lysine was indispensable to the young but not to the adult. Frazier et al.[16] demonstrated, however, that lysine was essential for growth of new tissue in the protein-depleted adult rat. Lysine is definitely needed for maintenance in the adult man[2] and in the adult dog.[6]

Internal supplementation may explain some of the marked effects of unbalanced mixtures of amino acids on the body. A large excess of methionine added to casein in the diet will cause loss of nitrogen from skeletal tissues of the rat but will result in the building up of liver and kidney tissue. Similarly, Whipple and associates[33] suggest that an incomplete protein can be supplemented from reserve stores to produce cell or plasma protein. It is possible, therefore, that some tissues are torn down, supplying amino acids, to build up others.

TABLE II*

Nitrogen Source	Day	Dog 83		Dog 84	
		UN, mg./day/Kg.	K	UN, mg./day/Kg.	K
Protein-free	0–3	85	....	66	
Casein hydrolysate	4	131	0.62	135	0.43
Casein hydrolysate	5	141	0.54	112	0.62
Casein hydrolysate	6	130	0.65	112	0.57
Casein hydrolysate	7	118	0.75	100	0.68
Protein-free	8–10	88	....	61	

* Nitrogen source, days on experiment, nitrogen intake (AN), urinary nitrogen (UN) and nitrogen balance index (K). K is calculated from the equation UN = (1 − K) (AN) + UNo. The nitrogen intake was obtained by intravenous feeding of 120 mg. hydrolysate nitrogen per day per Kg. of body weight at the rate of 2 mg. N per minute per Kg. UNo is the excretion of nitrogen on a protein-free diet.

Nitrogen Balance Indexes in Intravenous Feeding. Nitrogen balance indexes can be determined for protein hydrolysates fed intravenously as well as orally.[17] These indexes are calculated from the following equation which is derived from (1) UN = (1 − K) AN + UNo; (2) when UN is urinary nitrogen, K is the nitrogen balance index, (AN) is absorbed nitrogen and UNo is the excretion of urinary nitrogen on a protein-free diet. The data recorded in Table II illustrate the calculation of the index of an enzymatic casein hydrolysate from equation 2. The dogs were fed a protein-free diet (70 calories/Kg. of body

weight) until the urinary nitrogen excretion was relatively constant, collections being made over a three-day period to determine an average UNo. The hydrolysate was fed intravenously for the next four days, 120 mg. of N/day/Kg. of body weight being infused at the rate of 2 mg. N/min/Kg. One hour after the infusion the dogs received the protein-free diet to keep their caloric intake constant. After four days of infusion the dogs were fed the protein-free diet again for three days to determine another average value for UNo. The values for K were calculated using the first UNo with UN for the fourth and fifth days and the last UNo for the sixth and seventh days.

The daily variation in values for K can be very great in dogs depending upon a number of factors, many of them being unknown. In one dog, for example, a casein hydrolysate had an average index of 0.5 which decreased suddenly to 0 and then to negative values, body nitrogen being lost. The excess loss of nitrogen was associated with an infection, the disappearance of which resulted in a return to a normal index. Toxic substances or anything that alters metabolic processes can alter the retention of nitrogen by the animal. There is a great need to determine the factors, especially in the sick animal, which can effect this retention.

The indexes for the hydrolysate fed intravenously into the protein-depleted dog are greater than in the normal animal, showing greater nitrogen retention in the depleted animal. (Table III.) Similarly, Silber et al.[18] found that protein depletion increased the retention of amino acid nitrogen in the animal. The data in this table also illustrate the higher indexes obtained when the hydrolysates are fed orally than when they are infused intravenously. A different pattern of amino acids could be presented from the gastrointestinal tract than from the vein because of digestive and absorptive processes in the gut and of more direct action of the liver on the products absorbed from the intestine. Loss of amino acids or polypeptides by excretion in the urine will reduce the index of the hydrolysate fed intravenously.

The rate of excretion of α amino nitrogen, ammonia and urea nitrogen and other forms of nitrogen during the day of infusion are illustrated in Fig. 3. The first hour in this figure represents the rate of excretion of the various forms of nitrogen before the infusion was started. The infusions were given during the first to third hours. The black blocks represent the rate of excretion of α amino nitrogen; the blocks with slanted lines, the rate of excretion of ammonia plus urea nitrogen and the white blocks, the excretion of other forms of nitrogen. These data were obtained during infusion of a fibrin hydrolysate in which 57 per cent of the nitrogen was in the form of polypeptides.

The figure illustrates the marked rise above control values in the rate of excretion of α amino nitrogen and of ammonia and urea nitrogen during and after the infusion. The rate of excretion of α amino nitrogen fell rapidly toward control values within an hour after the infusion ended. The rate of excretion of urea and ammonia nitrogen continued to rise after the infusion, returning to control values several hours thereafter. The excretion of other forms of nitrogen increased also during and for

TABLE III*

NITROGEN BALANCE INDEXES OF PROTEIN HYDROLYSATES FED ORALLY OR INTRAVENOUSLY TO NORMAL DOGS OR INTRAVENOUSLY TO DEPLETED DOGS

Hydrolysate	Nitrogen Balance Index		
	Normal		Depleted
	Oral	Intravenous	Intravenous
Commercial hydrolysate	0.82	0.67	0.82
Casein hydrolysate	0.82	0.60	
Fibrin hydrolysate	0.81	0.66	
Fibrin (crude) hydrolysate	0.60	0.36	0.53

* Some of these data were taken from a paper by Allison, Seeley and Ferguson.[17]

several hours after the infusion. This increase was due to polypeptide nitrogen not utilized by the animal. Loss of amino acids and peptides (if the latter are present) through excretion in the urine are greater, the higher the rate of infusion. If the essential amino acids are well above threshold concentrations, however, the rate of infusion has no effect on the nitrogen balance index.

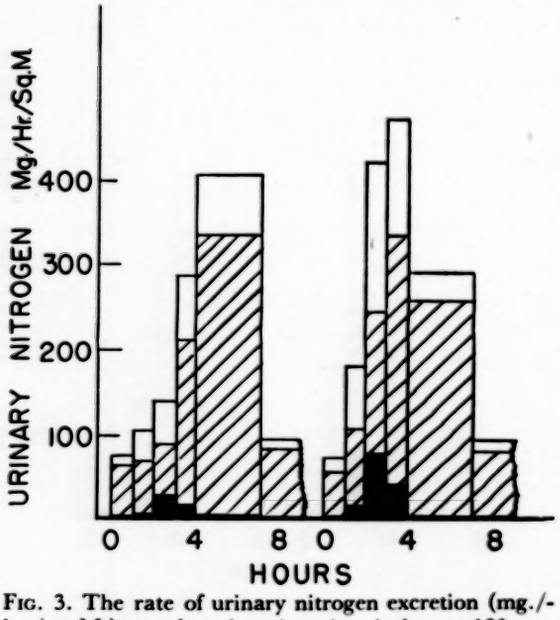

FIG. 3. The rate of urinary nitrogen excretion (mg./-hr./sq. M.) are plotted against time in hours; 120 mg. of hydrolysate nitrogen per Kg. of body weight were infused the first to third hours. The black blocks represent the rate of excretion of π amino nitrogen, the blocks with slanted lines the rate of excretion of urea plus ammonia nitrogen and the white blocks the rate of excretion of other forms of nitrogen.

Effects of Caloric Intake. Retention of nitrogen in the animal also is a function of caloric intake. The urinary nitrogen excretion increases, for example, in the dog[3] and in man[13] if the caloric intake is lowered below optimum. A reduction in caloric intake, therefore, increases the excretion of nitrogen from body stores. Bosshardt et al.[19] demonstrated that the growth of nitrogen in the tissues of the rat and the mouse was maintained over a range of caloric intake but that decreases below that range resulted in a reduction in the formation of new tissue. They pointed out that the excretion of body nitrogen may be increased by the reduction in caloric intake, leaving a smaller proportion of the absorbed nitrogen for the development of new tissue.

The nitrogen balance indexes of the dietary protein or hydrolysate are not altered in the dog until the caloric intake has been reduced to less than 50 per cent of normal.[4] This normal caloric intake varies with the breed and activity of the dog averaging 70 calories/Kg. of body weight. Some breeds, particularly the smaller active ones such as the fox terriers, require 100 or more calories/Kg. of body weight, but the critical caloric intake below which nitrogen retention falls rapidly is usually around 35 calories/Kg. A similar reduction in retention of dietary nitrogen with decreased caloric intake has been found in the rat by Willman et al.[20] and in man by Schwimmer and associates.[2] The latter workers demonstrated that young men fed a semisynthetic diet containing egg white retained the dietary nitrogen if the intake was 1,500 to 1,800 or more calories but did not do so on intakes of 900 calories. Retention of nitrogen was obtained, however, at the lower caloric intake if the nitrogen and fat contents of the diet were sufficiently high. Willman et al.[20] also reported that the retention of nitrogen in the rat was improved on a restricted diet if the fat content was high.

Benditt et al.[22] studied "the interrelationship between protein and caloric intakes and their influence upon the utilization of ingested protein for tissue synthesis by the adult protein-depleted rat." They also found a critical level of caloric intake below which the retention of nitrogen was restricted. This critical level was approximately 1,240 calories/sq. M./day. They concluded from their studies that "the fabrication of a kilogram of tissue on a growing rat and the reconstruction of a kilogram of tissue in the adult protein-depleted rat demand the same quantities of structural material and similar constructing energies." They concluded further "that the rate of protein utilization is independent

of the caloric intake at caloric intake levels above those which supply the needs for maintenance, synthesis, storage, and waste."[23]

Elman,[24] however, has pointed out that "fatty tissue may readily furnish a good deal of the daily caloric intake." He demonstrated in dogs "that the amount of energy supplied may be drastically reduced without leading to depletion of essential protein tissue, provided a sufficient amount of protein is given. Under these conditions the energy requirements are obviously made to come from tissue fat, whose depletion leads to no physiologic impairment."

Effect of Degree of Hydrolysis. The question is often asked as to whether or not a protein hydrolysate fed orally is utilized as well or better than the natural protein. The indexes of unsupplemented acid hydrolysates are always lower than the protein of which they are made because acid hydrolysis destroys essential amino acids such as tryptophane. Most acid hydrolysates can be reconstituted by addition of optimum amounts of tryptophane and sometimes methionine. There are data in the literature which support the belief that hydrolysis destroys some essential polypeptide or other constituent of the protein not identified as an amino acid. Miller, Robscheit-Robbins and Whipple[25] present data which can be interpreted to mean that there is some unidentified substance present in dietary proteins, absent in mixtures of amino acids, which effects the retention of nitrogen in the animal. Similarly, Womack and Rose[26] have evidence that protein may contain substances, not found in amino acid mixtures, which promote maximum growth of rats. Recently, Wooley[27,28] found one or more polypeptides called strepogenin in intact proteins essential for optimum utilization of nitrogen by the mouse. Frazier et al.,[16] on the other hand, found a mixture of amino acids just as adequate as natural protein for regeneration of tissue proteins in the protein-depleted rat. Chow, Allison and White[29] have demonstrated that the utilization of casein by the dog and rat is not altered by enzymatic hydrolysis, the hydrolysates having the same nitrogen balance indexes and growth-promoting values in dogs and rats as the unhydrolyzed casein. Enzymatic hydrolysis, which released at the most only 60 per cent of the available amino acids, did not alter the strepogenin content of the casein and would not necessarily alter other essential polypeptides. Complete hydrolysis might, therefore, have lowered the nutritive value by destroying these peptides. Experiments involving synthetic patterns of amino acids or reconstituted acid hydrolysate indicate, however, that peptides like streptogenin are not indispensable but may, at times, improve utilization of an amino acid mixture by increasing the nitrogen intake or by supplying an additional quantity of essential substances that cannot always be synthesized in adequate quantities by the animal.

Significance of a Positive Nitrogen Balance. Growth of new tissue, whether in the young or adult animal, cannot take place, no matter what the pattern of amino acids may be, unless sufficient nitrogen is given to place the animal in positive nitrogen balance. An examination of Figure 2 demonstrates that the largest positive nitrogen balances are produced in the protein-depleted dogs. The growth in nitrogen, in other words, continues in a linear fashion well on the positive side of nitrogen balance. Much more nitrogen is needed by a depleted than a normal animal, and much more can be fed to such a system before it is all wasted in catabolism. The more the protein stores are filled the less growth can be experienced in the region of positive nitrogen balance in the adult animal. Theoretically, if the stores are all saturated, the adult animal cannot be put into positive nitrogen balance. The aim in protein nutrition is to fill the stores so that they can be maintained by a relatively small daily intake of a good pattern of amino acids. Few animals are in that ideal nutritional state, most of them being deficient in tissue proteins some place in the body.

The data plotted in Figure 4 illustrate the facts (1) that there is an upper limit to the growth in nitrogen that can be obtained by feeding a protein source and (2) that a much greater maximum balance can be obtained with a good pattern than

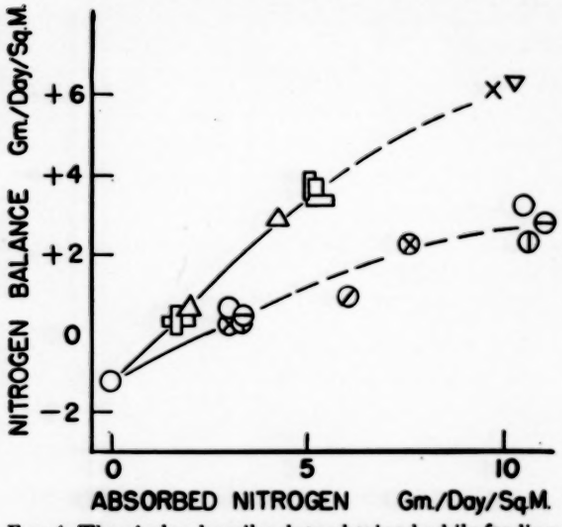

FIG. 4. The circles describe data obtained while feeding wheat gluten to protein-depleted dogs, the angular symbols describe similar data obtained while feeding whole egg. The data are expressed as Gm./day/sq. M. of body surface area.

with a poor pattern of amino acids. The angular symbols in this figure illustrate data obtained while feeding a dried defatted whole egg preparation to protein-depleted dogs. The maximum positive nitrogen balance that could be obtained by feeding this nitrogen source was approximately 6 Gm./day/sq. M. of body surface area. Feeding larger amounts than those required to produce the maximum, is not an efficient way to replete the animal. The circles represent data obtained while feeding wheat gluten to another group of depleted dogs. The maximum positive nitrogen balance that could be produced by this nitrogen source was less than 3 Gm./day/sq. M. Again there was no need to feed more than the amount necessary to produce this maximum. The filling of the protein stores with wheat gluten is, therefore, a much slower process than with the whole egg preparation. Each pattern of amino acids has an upper limit for utilization by the animal.

Effects of Depletion in Proteins. Depletion in proteins results in the general reduction in the so-called protein reserves of the body, in labile liver cytoplasm, in plasma albumin, in hemoglobin, in plasma gamma globulin and in the nitrogen of the other tissues of the body. The loss in liver nitrogen is rapid and marked when an animal is placed on a protein-free diet.[30–32] The total circulating plasma albumin decreases under a condition of nitrogen deficiency reflecting the loss of nitrogen throughout the body of the animal. There is, in other words, an interchange between the nitrogen of the body which is expressed as a dynamic equilibrium, a steady state which has been emphasized by the work of Whipple and associates.[33]

Total plasma proteins will vary approximately from 5.8 to 7.5 Gm. per cent averaging 6.5 Gm. per cent in an heterogeneous group of so-called normal dogs. Although plasma protein concentrations are not absolute measures of the magnitude of protein stores, values less than 5.8 Gm. per cent usually represent a state of depletion in proteins. The decrease of plasma protein below that value is a result of a decrease in plasma albumin and in the beta and gamma globulin fractions. The alpha globulin fractions, on the other hand, increase in concentration as the protein stores are depleted. One dog, for example, had the following percentages of plasma proteins under control conditions on an adequate diet: total plasma proteins, 6.0; albumin, 2.5; alpha globulins, 0.9; beta globulins, 2.0; gamma globulin, 0.6. After several weeks on a protein-free diet these values had changed to: total protein, 3.8; albumin, 1.0; alpha globulins, 1.6; beta globulins, 0.9; gamma globulin, 0.3. The electrophoretic patterns of plasma proteins from a dog before and after depletion and after repletion in proteins by feeding casein are illustrated in Figure 5.[34] The tall peak representing the albumin fraction is markedly reduced in the depleted dog and is returned to normal by repletion.

FIG. 5. Electrophoretic patterns (descending) of plasma from a dog before and after depletion in proteins and after repletion of casein. The numbers indicate the components: albumin 1; α_1 globulin 2; α_2 globulin 3; β_1 globulin 4; β_2 globulin 5; β_3 globulin 6; fibrinogen 7; γ globulin 8.These studies were done in cooperation with Dr. B. F. Chow of The Squibb Institute for Medical Research and the electrophoretic patterns were obtained by him.

Thus, the degree of depletion is correlated well with the fall in the albumin/globulin ratio because the albumin fraction is markedly reduced while the globulin fraction is not. The increase of the α-globulin fraction of the plasma is the result of the fall in plasma volume not of a rise in total circulating α globulin. The total amount of this globulin fraction rarely changes significantly in the dog until the animal has been so severely depleted in proteins that liver damage is quite marked; repletion is difficult, the animal often dying in the depleted state. The decrease in plasma albumin and increase in α globulin have also been found to be associated with malnutrition, tuberculosis or cancer in man.[35] The γ globulin fraction is reduced below normal in the depleted dog, a reduction which is accompanied by an increased susceptibility to infection. These infections can be treated and the growth of invading pathogens halted but the animal cannot develop a resistance to the invasion without repletion in proteins.

Associated with the decrease in plasma albumin in the depleted animal is a reduction in plasma volume and an increase in the extracellular fluid.[36] For example, one dog under control conditions had a plasma volume of 625 ml. and an extracellular fluid volume of 3,500 ml. Following depletion in proteins, the plasma volume had dropped to 502 ml. while the extracellular fluid volume had increased to 4,400 ml. Even with this marked increase in extracellular fluid, edema could not be detected clinically. Nutritionally edema is not clinically evident in dogs until it is severe.

Because of the fall in plasma volume, however, the plasma protein may be concentrated to such an extent that hypoproteinemia does not develop. The plasma protein concentration of a normal dog, for example, was 7.04 Gm. per cent. (Table IV.) The plasma volume was 430 ml., the total circulating proteins equaling 30.2 Gm. After depletion in proteins the plasma protein concentration was 5.94 Gm. per cent, still within the normal range. The relatively high plasma protein concentration was the result of the marked fall in plasma volume to 349 ml. The total circulating proteins had decreased to 19.5

TABLE IV*

	Plasma Protein, Gm. %	Plasma Volume, ml.	Total Circulating Albumin A, Gm.	Total Circulating Globulin G, Gm.	A/G
Control...	7.04	430	16.6	13.6	1.2
Depleted..	5.94	349	6.4	13.1	0.49
Repleted..	6.16	470	15.6	13.2	1.2

* Data to demonstrate that marked hypoproteinemia in the dog does not always accompany protein depletion. The effects of depletion and repletion on total circulating albumins, globulins and the A/G ratio are also recorded.

Gm., 6.4 of which was albumin and 13.1 globulin.

In their studies on the effect of protein depletion in dogs Whipple, Robscheit-Robbins and Miller[33,37] have used a so-called doubly depleted animal. This double depletion is produced by sustained bleeding of dogs fed a protein-free or low protein diet with adequate iron. The reserve stores of blood protein producing materials are depleted by maintaining levels of 6 to 8 Gm. per cent of hemoglobin and 4 to 5 per cent of proteins. They state that "the body guards jealously the fabrication of hemoglobin and, given a real need for both plasma protein and hemoglobin (anemia and hypoproteinemia of double depletion), the protein flow favors hemoglobin." They have also shown that doubly depleted dogs will continue to produce much plasma protein and hemoglobin for many weeks while being fed a protein-free diet. Thus, the blood proteins take priority over other tissue proteins, an example of the "ebb and flow" between tissue and blood proteins. The transformation of tissue proteins into blood proteins caused a loss in body weight, the average dog tolerates raiding of body tissue proteins from seven to eleven weeks.

The quantity of protein in the liver is lost most rapidly when animals are placed on a low nitrogen or protein-free diet. Liver function decreases in the depleted animal. Kosterlitz[32] demonstrated that this loss was associated with a reduction in liver cytoplasm and Li and Freeman[38,39] have shown that fatty livers developed in dogs fed a 33 per cent fat protein-deficient diet for ten to sixteen weeks. They also found the incidence of peptic ulcers high in protein-deficient dogs.[40] Armstrong and Estremera[41] found that bone atrophy develops in adult rats fed a protein-deficient diet. Corneal vascularization develops also in protein deficiencies, proving that corneal tissue like all other tissues of the body requires the proper daily pattern of amino acids in the diet to maintain its integrity.[42,43]

Weech[44] and Sachar et al.[45] have shown that there is a constant relationship between the loss from plasma proteins and from the rest of the body during protein depletion, for every Gm. of plasma protein lost approximately 30 Gm. are lost from other body tissues.

Repletion in Proteins. When the animal is repleted, nitrogen is replaced in the body tissue proteins and the plasma proteins in the same ratio of 30:1. This ratio is illustrated in Table v. These data were obtained on depleted dogs which were repleted for thirty days with whole egg protein. The difference between ingested and nitrogen excreted is recorded as nitrogen gained. The body nitrogen gained by these dogs over the thirty-day repletion period varied from eighty-seven to one hundred, averaging 93.8 Gm./sq. M. body surface area. The average plasma protein concentration at the end of the repletion period was 6.2 Gm. per cent which is an average for most normal dogs. The total increase in plasma protein nitrogen during the repletion period varied from 2.1 to 4.3, averaging 3 Gm. per sq. M. This increase in plasma protein nitrogen represented an average of 3.2 per cent of the body nitrogen gained. Thus, approximately one-thirtieth of the

TABLE V*

Dog No.	Nitrogen Ingested, Gm./sq.M.	Nitrogen Excreted, Gm./sq.M.	Body Nitrogen Gained (B.N.G.) Gm./sq.M.	Plasma Protein Nitrogen Gained (P.N.G.) Gm./sq.M.	$\frac{\text{P.N.G.}}{\text{B.N.G.}} \times 100$ Per Cent
28	189.0	88.6	100.4	3.06	3.05
42	174.0	81.0	93.0	2.83	3.04
44	192.0	95.8	96.2	2.84	2.95
63	176.2	83.6	92.6	4.29	4.63
74	175.1	88.2	86.9	2.11	2.43

* Dogs depleted in proteins were repleted for thirty days with whole egg protein. Nitrogen ingested, nitrogen excreted and body nitrogen gained during this repletion period are recorded. Plasma protein nitrogen gained and the per cent of the body nitrogen gained which is represented as plasma protein nitrogen are listed.

nitrogen gained was represented as plasma proteins, principally albumin.

The type of protein found in the tissue and in the plasma can vary, however, according to the pattern of amino acids fed to the animals. Seeley[46] found, for example, that the oral feeding of beef serum protein favored repletion of plasma albumin while casein promoted the formation of both albumin and globulin. Similar results were reported by Holman et al.[47] and by Madden and Whipple.[48] Chow et al.[49] demonstrated that oral administration of a casein hydrolysate brought about an increase in both albumin and globulins, increasing the globulins even above normal values in dogs. Lactalbumin hydrolysate, on the other hand, favored regeneration of the albumin fraction. It has been pointed out previously that imbalances between the essential amino acids can bring about internal supplementation, leading to the reduction of one kind of tissue nitrogen and to the building up of others. Cannon and associates have demonstrated that the same amino acids which are essential for growth in the rat are also indispensible for repletion of body tissue in the protein-depleted rat although the proportions vary according to the state of depletion and physiologic state of the animal. Cannon[50] emphasized that all of the amino acids necessary to synthesize tissue protein must be present simultaneously, in adequate amounts and in the proper proportions. The dietary essential amino acids become a part of the dynamic equilibrium which characterizes protein metabolism, repletion of tissue proteins being a function of the pattern of amino acids introduced into this equilibrium.

COMMENTS

The protein stores are the proteins of the tissue cells and the fluids which bathe them, forming a dynamic equilibrium so that the body, as a whole, is a reservoir for the nitrogen needed to maintain the integrity of its protoplasm. These stores are reduced in malnutrition or disease and in their reduction the body loses capacity to repair damage, to build antibodies and to maintain the mechanisms which create barriers to destructive forces. It is a function of the diet, of protein therapy, to replenish these stores. There are no reserves of essential amino acids which can be drawn upon to supplement an inadequate diet without breaking down body proteins so that dietary sources lacking one or more of these acids cannot fill the reservoir. It is filled by simultaneously presenting to the body all of the essential amino acids in the proper proportions and amounts. Growth and regeneration of destroyed tissues take place only in the presence of sufficient nitrogen to create a positive nitrogen balance. Dietary sources for nitrogen whether they are proteins, hydrolysates or mixtures of amino acids are evaluated, therefore, according to their ability to promote the maintenance, repair and growth of body tissues.

The protein stores are reduced in the depleted state and they are different in character than in the normal individual. Less dietary nitrogen is needed to maintain the depleted than the normal state, and the potentialities for growth increase upon depletion. Indeed, the degree of depletion can be estimated by the magnitude of positive nitrogen balance that can be produced. It is the function of protein therapy to provide an optimum pattern of amino acids to fill these stores as uniformily as possible. There is a maximum rate at which each protein or pattern of amino acids is capable of promoting the growth in nitrogen; feeding more than the amount necessary to produce the maximum rate is inefficient and may at times place a catabolic and excretory burden upon the individual.

The reservoir of body nitrogen, being composed of the tissues, is a series of compartments with differing capabilities for supplying nitrogen to the metabolic pool. Some tissue proteins, such as the albumins, are more labile in providing nitrogen to this pool than are others such as certain globulins. Different amino acid patterns

can favor the filling of one compartment over another, even depleting one while filling a second. Thus, different amino acid patterns can do different jobs in the body.

Finally, it cannot be overemphasized that protein therapy is an integral part of an overall diet therapy. Energy, derived from carbohydrates and fats, is needed to drive the mechanisms which rebuild or develop new living tissues. Fats and carbohydrates spare dietary and tissue nitrogen. Enzymes are built from amino acids, with vitamins as well as certain amino acids providing the active spots for catalysis. A vitamin deficiency can lead to marked reduction in protein stores. All constituents of the diet, therefore, including the minerals and water, play important roles in the maintenance, repair, and growth of living tissues and in the promotion of the well being of the animal. A new era of integration is developing in nutrition.

SUMMARY

1. The protein stores of the animal are the labile cytoplasmic proteins in the tissues and body fluids, cellular nitrogen being drawn upon to maintain the nitrogen integrity of essential tissues.

2. The amount of nitrogen excreted from the protein stores during the feeding of a protein-free ration decreases as the stores are depleted. Less dietary nitrogen is needed to maintain nitrogen equilibrium in a depleted than in a normal animal.

3. The relationship between absorbed nitrogen and nitrogen balance is linear in the region of negative nitrogen balance becoming curvilinear in the region of positive balance. The slope of this line, called the nitrogen balance index, is a function of the retention of nitrogen in the body of the animal, the index increasing as the retention increases. The index evaluates the retention of dietary nitrogen for the overall filling of the protein stores of the animal.

4. As the protein stores decrease the linear relationship between nitrogen balance and absorbed nitrogen extends further and further into the region of positive nitrogen balance, the greater the positive balance the greater the degree of depletion in proteins. Different patterns of amino acids fill the stores at different rates. Feeding a protein source above an amount which produces maximum filling, is inefficient.

5. Supplementation of proteins and protein hydrolysates with amino acids can improve the indexes but imbalances produced by the addition of abnormal amounts of amino acids may cause loss in body nitrogen. It is possible under conditions of imbalance to build up one tissue while another is being torn down.

6. Hydrolysates or amino acid mixtures fed intravenously have a lower index than when fed orally. The higher oral index is due, in part, to the effects of digestive and absorptive processes in the gut and more direct action of the liver on the products absorbed from the intestine. The increased urinary excretion of amino acids and peptides following intravenous feeding does not usually affect the index significantly.

7. The retention of dietary nitrogen is a function, too, of caloric intake. There is a critical level of caloric intake (approximately 50 per cent of adequate) below which the retention of nitrogen is markedly reduced.

8. The retention of nitrogen fed orally is not affected by the degree of enzymatic hydrolysis of the protein.

9. Depletion in proteins results in reduction in protein stores of the body, labile liver cytoplasm, plasma albumin, hemoglobin, plasma gamma globulin and in the nitrogen of the other tissues of the body. Thirty times as much nitrogen is lost from the body tissues as from the plasma. A shift in body fluids accompanies the depletion, resulting in a nutritional edema accompanied usually by a fall in plasma volume. The decrease in plasma volume can be so great that hypoproteinemia does not develop.

10. When the animal is repleted, the nitrogen is retained in the body tissue proteins and plasma proteins in the ratio of 30:1. Restoration of tissue nitrogen is a

function of the patterns of amino acids which are given, different patterns producing different rates of repletion of the various protein stores.

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Combined Staff Clinics

Peripheral Vascular Disease

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. FREDERICK K. HEATH: The subject of this clinic is a consideration of the genesis and therapeutics of arterial vasospasm in peripheral vascular disease but before beginning the discussion a few introductory remarks may be in order.

Despite the fact that the extremities make up about 35 per cent of the total body mass and 65 per cent of the body surface, peripheral vascular disease has never been a popular medical specialty. This stepchild of medicine remains largely a subject for clinical observation, statistical analysis and shotgun therapy. Emphasis has been placed on empiricism, dogmatism and treatment so that the literature is voluminous, conflicting and unreliable. Clinical investigators who have turned their attention to the solution of vascular mechanisms have been few in number; the investigative literature dealing with functioning of the blood vessels and blood flow in quantitative terms is small indeed and prior to 1930 almost non-existent. Not only do the diseases of the vessels seem to present insoluble problems of etiology and rational therapy but because of the lack of adequate investigative methods they often defy serious analysis.

What are those conditions so loosely assigned to the limbo of peripheral vascular disease? In a general way one may delineate two main groups: (1) those resulting from organic disease of the blood vessels causing narrowing of the lumen with reduction in blood flow of a permanent character and (2) those showing no organic change in the blood vessels but characterized by an obvious decrease in blood flow which is reversible and due to temporary narrowing of the lumen by spasm. The first group includes arteriosclerosis and thromboangiitis obliterans, each of which may have a superimposed spastic component. The second group is comprised of Raynaud's syndrome, scleroderma, livedo reticularis, acrocyanosis, and spastic phenomena associated with cervical ribs, scalene syndrome, embolism, thrombosis and thrombophlebitis, Sudeck's atrophy, shoulder-hand syndrome and trauma.

Since all these states are associated with a reduction in the rate of arterial blood flow, it becomes important to examine the methods available to measure this factor. Qualitative information is easily obtained. The color of the skin depends on the state of the capillaries and first venous subpapillary plexus, the rate at which these vessels are filled or emptied and upon the oxygen saturation of the blood. The temperature of the skin is an index of the rate of blood flow through it. Thus marked narrowing but not obliteration of a main arterial trunk to an extremity produces pale, cold skin. On dependency, redness and then cyanosis may be added if not already present. With sympathetic activity, in certain spastic states, there may be sweating as well. Attendant upon the collateral supply, the level at which the arterial inflow is reduced may be determined by simple inspection or by noting the skin temperature or the fullness of the pulse of the artery supplying the extremity.

With involvement of arteries of smaller caliber, essentially the same picture results. Thus in Raynaud's syndrome spasm of the digital arteries first produces pallor and coldness of the skin of the fingers, the blood pools in the capillaries and becomes anoxic,

with resulting dilatation of the capillaries and venules and the appearance of a blue color. Immediately following the spasm, when the arterial inflow returns to normal, the skin is hot and red since the wide open minute vessels do not immediately regain their tone and so become filled with relatively fast-moving oxygenated blood.

The cold, wet, blue hands and feet of acrocyanosis are thought to result from spasm of the arterioles and small venules with capillary dilatation and stagnation of the blood. The mottled blue skin of livedo reticularis is similarly believed to be the result of spasm of the smaller vessels.

Much information, therefore, can be gained by visual and tactile means. Some of the more objective procedures furnish relatively little more information. Thus measurements of skin temperature simply put into objective terms what may be somewhat less accurately gauged with the hands and like the more simple procedures it furnishes information only in regard to the blood flow to the skin. To interpret differences in skin temperature before and after a procedure designed to produce vasodilatation it is essential that the determinations be made under identical conditions of environmental temperature in which the patient is allowed at least thirty minutes to approach a state of equilibrium. Even here the skin temperature of the digits may vary widely, dependent upon shunting in response to a multitude of factors such as emotion, smoking and ingestion of food. Under standard conditions, i.e., room temperature 25°C., average values for the fingers are in the vicinity of 32° to 35°C., with the toes somewhat lower but usually above room temperature. Nearer the trunk, skin temperatures are higher.

Oscillometry is designed to measure the volume of the pulses. The instrument consists of a sensitive needle which fluctuates over a unit scale in response to the arterial pulsations in an extremity transmitted through a pressure cuff, the principle resembling that of the ordinary blood pressure manometer. However, in the case of the oscillometer readings are taken over a variety of pressures and only the maximal deflection is significant. Normal values differ from patient to patient, from instrument to instrument and from observer to observer. The range in the thigh may approximate 4 to 15 units, the leg 3 to 12, the ankle 1 to 10 and the foot from 0 to 3; readings in the arms are comparable to the legs. The oscillometer is often expected to yield more information that it can. It simply measures the amplitude of the pulsation in relatively large vessels and hence may be useful to verify the presence or absence of a doubtful pulse or to mark the level of arterial obstruction. To interpret the size of the excursion in terms of blood flow is erroneous since the oscillometric readings may be small or absent with obstruction of a main artery yet adequate small vessel collateral flow may exist; conversely, with marked vasodilation increase in oscillometric readings may occur with actual reduction in total flow due to a disproportionate increase in the backflow phase.

Arteriography with diodrast or other contrast medium is an elaborate, expensive method of outlining the blood vessels. In certain instances, for example the demonstration of aneurysm or arteriovenous communications, it may be most helpful. On the other hand, it suffers from two main objections: the distinction between spasm and thrombosis is difficult and it yields no information as to the rate of blood flow.

One interesting method of obtaining qualitative although not quantitative data on blood flow is the use of radioactive sodium intravenously with subsequent periodic determinations of the Geiger count over certain areas of the extremities. In this fashion a curve may be obtained (Fig. 1) which may be useful as a baseline to estimate objectively the effect of therapeutic or investigative procedures on blood flow in any given area.

Quantitative measurement of the blood flow to the extremities is difficult. The use of A-V O_2 difference is not applicable to

the limbs because of the extensive and variable shunting which takes place in the hand and foot and which is not subject to control or measurement. At the present time the venous occlusion plethysmograph, which is slow and cumbersome and can be used only in the resting state, furnishes the most reliable quantitative results. This instrument consists of an insulated watertight shell shaped to contain a part of an extremity and designed to record the increase in distal limb volume which occurs when the venous return is obstructed proximally by a pressure sufficient to occlude the venous outflow but not the arterial inflow. The results are recorded with reference to standard room and bath temperatures in terms of cc. of blood flow per minute per 100 cc. of limb volume. Obviously, the plethysmograph may be adapted to segments of a limb in order to obtain the flow in certain areas. With it much valuable information has been obtained. Table I[1] indicates the approximate blood flow in the extremities in the normal resting state and emphasizes the volatile nature of the shunts.

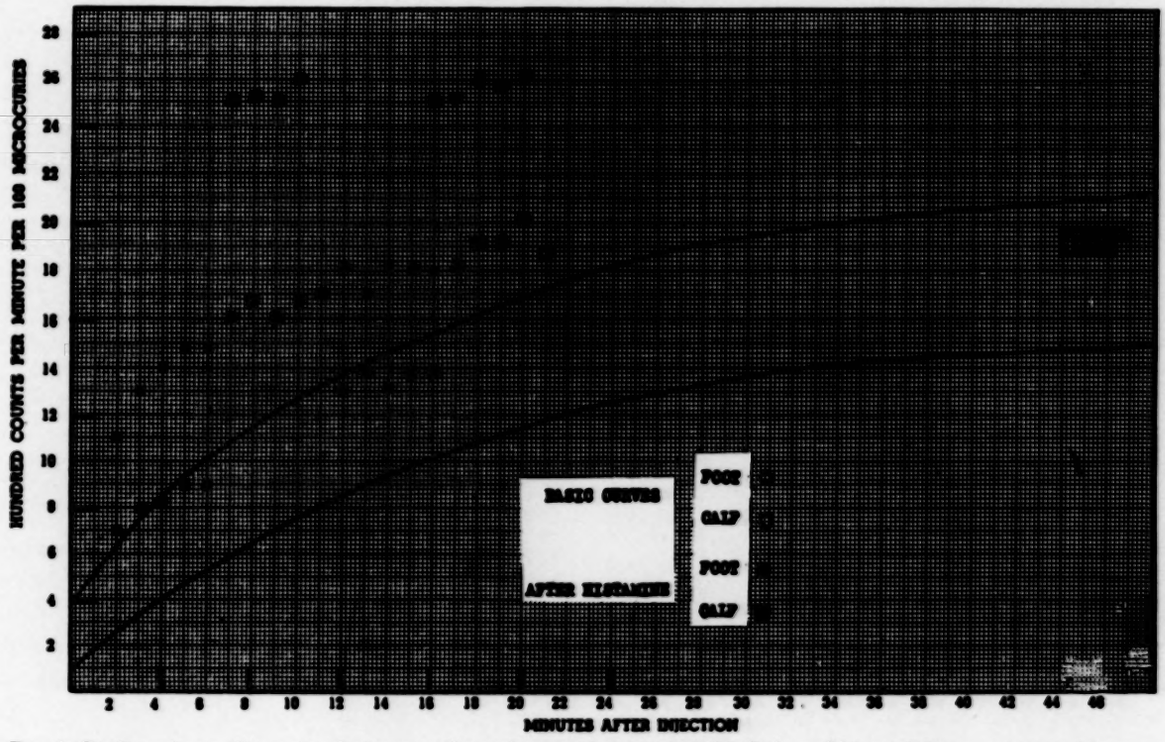

FIG. 1. Radioactive sodium circulation test shows how an intra-arterial infusion of histamine can cause an increase in the Geiger count over the foot and calf of a patient with arteriosclerotic endarteritis obliterans of the popliteal artery.

TABLE I
BLOOD FLOW IN CC./MIN./100 CC. LIMB VOLUME; ROOM TEMPERATURE 25°C.

	Bath Temperature	
	32°C.	43–45°C.
Finger	15–40	90.
Hand	9.3–2.1	22.
Forearm	1.8–0.7	7.9
Foot	1.2 to 2.8	18.1
Leg	1.4–0.5	3.6

No simple method yet available enables one to differentiate between blood flow to skin and that to muscle, a point which is significant in the problems of intermittent claudication. In such an instance use of a standard walking tolerance test gives the

[1] ABRAMSON, DAVID I. Vascular Responses in the Extremities of Man in Health and Disease. P. 80. Chicago, 1944. University of Chicago Press.

best information although if the total blood flow to a segment of an extremity is known it may be possible from anatomic considerations to approximate the proportional flow. Thus it has been shown by Abramson[2] that in the finger almost all the blood flow is through skin, in the hand the skin predominates 2:1 and in the forearm muscle predominates about 4:1. The foot resembles the hand while in the leg, muscle is even more predominate than in the forearm.

Recently Barcroft and Edholm[3] have produced vasoconstriction of the skin by adrenalin iontophoresis and then measured the increased blood flow of the sympathetic supply after block by procaine. Using this method and the anatomic data of Abramson, they estimate that blood flow to forearm muscle is doubled following removal of vasoconstrictor tone.

STUDENT: How does one differentiate clinically between organic obstruction to blood flow and spasm?

DR. HEATH: The most reliable method is by measurement of blood flow or exercise tolerance before and after procaine block of the regional somatic or sympathetic pathways. Dr. Bridges will discuss some of these problems from the point of view of the neurosurgeon.

DR. THOMAS BRIDGES: Raynaud's disease is the most characteristic example of peripheral vascular disease due to vasospasm. The smaller arteries of the distal portion of the extremities are most often the site of this intense vasospasm. However, arteries of the head and viscera may be involved. The involvement is symmetrical, that is, symptoms occur simultaneously in both hands or both feet. There is no occlusion of arteries or arterioles, at least early in the disease. The vasospasm causes coldness, cyanosis and, ultimately, tissue breakdown, gangrene, scarring or scleroderma. Cold temperatures and emotional crises aggravate the vasospasm. Women are affected primarily, the disease occurring rarely in men.

A typical case history is that of a thirty-eight year old divorcee who was admitted to the hospital complaining of aching and burning pain in both hands, of four years' duration, sometimes better and at other times much worse. Upon examination both hands were cold to the touch and there was a cyanotic hue to the fingers. All of the fingers had atrophic, shiny skin and both hands were constantly moist. Exposure to cold and emotional upsets resulted in blanching of the terminal phalanges. Over the tips of two fingers of each hand were small areas of dry, superficial ulceration which had appeared during the preceding three months. Stellate ganglion novocain block was effective in increasing the temperature of the corresponding hand and changing the slight cyanosis to a pink color. Bilateral thoracic preganglionic sympathectomy has been effective in maintaining good color and freedom from pain during the past winter.

Vasospasm of intensity almost equal to that seen in Raynaud's disease is encountered in an extremity in which there has been sudden occlusion of a major artery or vein. The occlusion may be due either to embolus or thrombosis or to trauma involving the vessel. The vascular tree may be quite normal prior to the sudden accident. The vasospasm is a primary neurovascular reflex, the stimulus arising from the area of vascular injury and sending impulses by way of viscerosensory nerves to the cord. The effector arc of this reflex is by way of the vasoconstrictor sympathetic nerves. Mass discharge is rarely seen and the vasospasm is generally limited to the extremity with the injured vessel. The usual signs of vasospasm occur: coldness, cyanosis, increased moisture of the skin. Oscillometric readings and arterial pulses are depressed by occlusion of a major artery but may not be depressed by the vasospasm of small vessels secondary to venous thrombosis or thrombophlebitis.

[2] ABRAMSON, D. I. and FERRIS, E. B., JR. Responses of blood vessels in the resting hand and forearm to various stimuli. *Am. Heart J.*, 19: 541, 1940.

[3] BARCROFT, H., ET AL. On sympathetic vasoconstrictor tone in human skeletal muscle. *J. Physiol.*, 102: 21, 1943.

Acute thrombophlebitis is accompanied by varying degrees of vasospasm more pronounced distal to the area of phlebitis.

A typical case history is that of a fifty-three year old man who was admitted to the hospital with marked bilateral varicosities. On the third hospital day, while on conservative treatment, the right leg suddenly became pulseless, cold, cyanotic and slightly painful. No arterial pulses were felt. A diagnosis of arterial thrombosis close to the iliofemoral junction was made. Right lumbar novocain sympathetic block was performed at the level of the first and second lumbar ganglia. Within thirty minutes the right foot became dry, slightly pink and more comfortable. The superficial foot veins dilated and the skin temperature rose 3°C. Arterial pulses were still absent. The block improved circulation to this extremity by opening collateral arteriolar connections.

It is interesting to speculate on the significance of this vasospasm secondary to blood vessel disease which seems so deleterious to the individual. It should be remembered that this reflex mechanism would be effective in decreasing blood loss from laceration or crush injuries involving major vessels and as such is a primary defense mechanism. If wound repair is rapid, collateral and primary circulation is restored before this vasospasm can produce serious consequences. It is probably a more valuable reflex system in lower animals.

Closely related to the vasospastic phenomena seen with direct vascular injuries are those grouped together under the term reflex sympathetic dystrophies. The most common examples of this group are traumatic arthritis (or Sudeck's atrophy) and the shoulder-hand syndrome. In these, vasospasm is generally less intense but more chronic than that which occurs after sudden vascular insult. The stimulus for this vasoconstriction arises from injury to a joint. The injury is generally mild, being only a strain or an acute articular inflammatory reaction of short duration. In addition to the usual signs of vasospasm there is overactivity of sweat glands with marked sweating over the distal part of the involved extremity. In cases of Sudeck's atrophy these changes are apparent in the foot and lower leg and most often follow a mild sprain or ankle "strain." The shoulder-hand syndrome is one in which evidence of sympathetic overactivity is seen in the hand and forearm following arthritis or bursitis of the shoulder, occasionally also after myocardial infarction.

A typical case of Sudeck's atrophy occurred in a nineteen year old seaman who was first seen six months after spraining his right ankle when he missed a step while descending a ship's ladder. X-rays had been negative for fracture or joint separation. He was able to walk for two days after the injury but was unable to bear weight on this ankle subsequently, despite intensive physiotherapy, strapping, casts with walking calipers and the like. At the time of our first examination the right foot was slightly swollen to above the ankle. The foot was very moist, cold and slightly cyanotic. There was no active motion at the ankle and passive motion was extremely painful. The patient refused to attempt to bear weight on this foot. X-rays revealed osteoporosis of the bones of the foot and lower leg. Novocain sympathetic block allowed slight passive ankle motion without pain. Two days after sympathectomy weight bearing was permitted and three weeks later complete motion of the ankle and full weight bearing had been restored. At that time the foot was dry, warm and pink.

A second group of vasospastic disorders which have been considered a type of reflex sympathetic dystrophy are those associated with spinal cord and peripheral nerve diseases. Poliomyelitis, peripheral nerve injuries, cervical rib compression of the brachial plexus and spinal root compression by herniated nucleus pulposus are among the common antecedent conditions for this type of vasospastic disorder. Pain is the presenting symptom and is of the "cramp-like" type, generally called intermittent claudication. This pain occurs either after exercise or when the patient is asleep. It is

considered to be due to a relative increase in demand for blood supply in the face of an inadequate circulation in the muscle groups involved in the cramps. Actual tightening of the muscle can be seen and felt. Unlike Sudeck's atrophy, evidence of sympathetic overactivity or of circulatory impairment may be absent or less striking in these cases and there is generally no osteoporosis.

A typical example of this type of reflex sympathetic dystrophy was encountered in a thirty-eight year old naval officer who had had a herniated nucleus pulposus removed, with relief of severe sciatic pain. Subsequently he developed cramping pain in the calf muscles of the leg, previously the site of sciatic pain. These cramps occurred at night and after walking two or three blocks. Physiotherapy and cessation of smoking did not influence this complaint over a six-month period. Right lumbar novocain sympathetic block gave complete relief for twenty-four hours. Lumbar sympathectomy has been effective in relieving the cramps for one and one-half years. At no time was this extremity cyanotic or cold and there was no osteoporosis. Excessive sweating of the right foot had been noted on occasion.

Causalgia has been listed as a form of reflex sympathetic dystrophy. The chief characteristic of this disorder is constant burning pain in the involved extremity. The disorder may follow nerve, blood vessel or soft tissue injury. Various degrees of vasospasm may be present. Pain is the main component. It is aggravated by touch and relieved by keeping the hand cold and wet. Causalgia is mentioned only for the sake of completeness. While it is frequently relieved by sympathetic block or surgery, the mechanisms involved have not been worked out. However, one possible mechanism may be release of spasm of the arteries supplying the cords of the brachial or lumbosacral plexus or of the median or sciatic nerves. All of these structures possess an arterial supply made up of small arteries roughly comparable to digital arteries in size. "Tingling," a form of hyperpathia to touch, was demonstrated by Sir Thomas Lewis to occur following interference with arterial supply to the nerves of the forearm and hand, and a "causalgia-like" syndrome has been observed in the lower extremities of patients in whom aneurysms of the abdominal aorta have been wired, and in whom the procedure has resulted in definite impairment in blood flow to the lower extremities. It would seem that the hyperpathia and constant burning pain were due to a conduction defect over the involved peripheral nerve or plexus and that release of vasospasm or improvement in collateral supply may often restore normal conduction with the relief of pain symptoms.

It might also be pointed out that oscillometric readings may not be appreciably altered in causalgia or other vasospastic states. Oscillometric excursions are derived from pulses in large arteries, the walls of which consist of a relatively large adventitial layer and proportionately small, smooth muscle coat so that even the most intense vasospasm could not result in collapse of the vessel or total obliteration of its lumen. Arteries such as the radial at the wrist, the digital arteries or the artery of the sciatic nerves have a greater proportion of smooth muscle and less fibrous tissue in relation to the diameter of the lumen, and when these vessels go into spasm the lumen may be almost completely obliterated. This may well be one reason why the vasospastic features of Raynaud's syndrome involve the digits, and why in causalgia one would not obtain significant changes in oscillometric readings.

Chronic ulceration of the lower extremities is most often seen as a result of circulatory impairment frequently secondary to deep vein occlusion and associated with varicose veins. In such cases the foot distal to the ulceration is moist, cool and cyanotic. Trophic ulceration secondary to cord or peripheral nerve injuries is accompanied less often by these vasospastic changes.

A fifty-eight year old retired naval chief was admitted with a large, chronic cutane-

ous ulcer located just above the medial malleolus of the right foot. The lesion was 3 inches in size with a base of infected, pale granulating tissue and slough. Arterial pulsations were present in the right dorsalis pedis but absent over the posterior tibial artery. There were extreme varicosities of both legs. The right foot distal to the ulceration ached and was cyanotic, cold and moist. With conservative measures, the ulcer became slightly larger over a period of six weeks. The right foot became warmer after a lumbar novocain sympathetic block. Four weeks after right lumbar sympathectomy the ulcer had healed.

These cases may be considered to be a form of reflex sympathetic dystrophy in which the stimulus for the vasomotor reflex arises in the skin lesion, or they may be a form of local vasoconstriction due to humoral or toxic effects from a chronically infected superficial lesion.

Thromboangiitis obliterans (Buerger's disease) and arteriosclerosis are the most frequently encountered types of peripheral vascular diseases occurring in our clinic population. For the most part there is little or no vasospasm in such disorders. When arteriosclerosis is complicated by diabetes, vasospasm practically never exists. The major peripheral vessels are involved; accordingly, vessel pulsations, as determined by palpation or oscillometry, are depressed or absent. Attempts to improve circulation by sympathetic block are frequently unsuccessful. However, upon occasion (about 10 per cent of the cases) there is a striking degree of vasospasm. Such patients usually have aggravation of their intermittent claudication on exposure to cold, feel better in a warm environment and can increase their activity after interruption of the sympathetic outflow.

A sixty-three year old man in the Vascular Clinic with the complaint of cramping pain occurring in one leg after walking five blocks, is being studied. His pain is relieved by standing still for one minute. There was a history of myocardial infarction. All peripheral vessels were thickened. Pulsations over the foot arteries were absent. Calcification of the arteries of both legs was extensive, as shown by x-ray. Following right lumbar novocain block, there was a rise of 4°C. in skin temperature over the toes. For four weeks after this block the patient doubled his walking tolerance; the pain was less intense when it appeared and the pain was relieved by standing for a few seconds. Subsequently he lost this good response and returned to his preblock state. There was no change in oscillometric readings at any time during this period. Incidently, this is the longest effect we have observed to follow one novocain block.

DR. EDMUND N. GOODMAN: At St. Albans Naval Hospital we have had opportunity to observe many patients with thromboangiitis obliterans. It is our opinion that many of these patients have increased vascular tone and can be significantly improved by sympathectomy. Nineteen patients so treated have remained greatly improved for a period of two years.

STUDENT: What about morbidity and mortality in the various types of sympathectomy and procaine blocks?

DR. BRIDGES: Thoracic and lumbar sympathectomies carry no mortality. These patients may anticipate hospitalization of two to three weeks. They may expect to return to work two to three weeks after operation.

Procaine blocks have been reported to have resulted (rarely) in unexpected demise during the block. Whether these accidents are due to procaine sensitivity or to inadvertent injection into an artery or vein is often difficult to determine from the reports given.

Procaine block of the stellate ganglion may be followed, on occasion, by pneumothorax. This is generally small, producing pain as the only symptom. When extensive, hospitalization and aspiration of the air may be required.

DR. HEATH: Many patients with vasospastic phenomena have been noted to exhibit neurotic personality traits. It there-

fore seems proper to inquire into the psychologic mechanisms of vasospasm. Dr. Daniels will present the general psychosomatic approach to these diseases.

DR. GEORGE E. DANIELS: It is hardly necessary to point out that peripheral vascular changes occur in relation to emotion. We continually see evidence of this in the blush of embarrassment, the flush of anger or the blanching from fear. Clinical and experimental studies show that under such states of emotion internal organs, as well as exposed parts of the body and the limbs, show similar vascular changes. The subject with a permanent gastric fistula reported by Wolff and Wolf[4] reflected parallel simultaneous changes in his face and gastric mucosa.

The best documented evidence of changes in peripheral circulation due to emotional changes has been gathered by Mittelmann and Wolff.[5] Under carefully controlled conditions 203 observations were made on forty-seven subjects, nineteen males and twenty-eight females. For some of the subjects an experimental situation was set up through the discussion of distressing life situations, reading of moving literature or requiring the patient to solve difficult problems under pressure. Other subjects were followed continuously during psychotherapy and circulatory changes in response to spontaneous emotional productions were registered. With both experimental and psychotherapeutic approaches, there was an immediate drop in skin temperature, reaching a maximum in some subjects of 13°c. whenever the subjects were placed in a distressing situation. Although great variations were observed in the different subjects, changes were constant for any one individual. In the entire series of experiments there were only three exceptions occurring in two subjects.

Mittelmann and Wolff found essentially no difference in the skin reaction of the patient with Raynaud's disease as compared with that of the other subjects except that the Raynaud patients showed blanching, pain and ulceration in the presence of lowered temperature. They found, as has been observed by others, that neither lowered temperature alone nor emotion alone produces these severe symptoms. A combination of the two is necessary. This has important implications for psychotherapy as well as for general medical management of such cases.

In the Raynaud patients who had undergone sympathectomy there were no local changes in relation to emotion. Surgery in such cases must be considered palliative and cannot be expected to change the personality aspect of the fundamental problem. Registration and discharge of tension, having been cut off through one route, may appear as a disturbance elsewhere. This was illustrated in a patient with Raynaud's disease who following sympathectomy developed a peptic ulcer. In many cases of this condition, before the final appearance of severe symptoms, there is evidence of a long history of emotional conflict. Raynaud, in his original article (1874), correctly appraised the situation: "In the present state of our knowledge, local asphyxia of the extremities ought to be considered as a neurosis, characterized by enormous exaggeration of the excito-motor energy of the gray parts of the spinal cord which control the vasomotor innervation."

Psychiatric treatment of patients with Raynaud's disease is often indicated, particularly in the early stages. The patient generally gives a history of early rejection by the family, with consequent basic insecurity, particularly in the face of crises. With psychotherapy, these patients often show direct registration of their return of confidence and feeling of support by a sensation of warmth in the extremities as contrasted with the shunting off of the circulation during periods of emotional withdrawal. The emotional component of Raynaud's disease should be evaluated

[4] WOLFF, H. G. and WOLF, S. G. Human Gastric Function. London, 1947.

[5] MITTELMANN, B. and WOLFF, H. G. Affective states and skin temperature: experimental study of subjects with "cold hands" and Raynaud's syndrome. *Psychosom. Med.*, 1: 271–292, 1939.

as a part of any thorough work-up. The severity and chronicity of the condition deserve a trial at psychotherapy if there is indication of an associated conflict.

Such conditions as Buerger's disease and diabetic atheromatosis have not been sufficiently studied to determine whether emotional factors play any part. If so, this presumably would be reinforcing a primary organic disease. Trench foot in the last war and traumatic arteriospasm in this war appear to be related to the reaction of certain constitutions under emotional stress plus injury to the part. In a recent article by Foisie[6] the presence of tension states associated with arteriospasm was postulated as a likely explanation of the disproportion between severity of the reaction and superficiality of the wound. The severity and destructiveness of the reactions, once under way, would indicate that preventive psychotherapeutic measures, applied as early as possible, might be very worth while.

Dr. Isidore Mufson: In connection with Dr. Daniels' remarks concerning the interplay of emotional forces and peripheral blood flow we have been using radioactive tracers to study these interesting phenomena. We also find that the mere discussion of a distressing life situation causes vasospasm and a drop in the temperature of the skin. It requires no great imagination to recognize that during the patient's actual experience of these same situations an even greater vasospasm and drop in temperature may be produced. Since these psychologic disturbances are chronic, their total effect is equal to the results of a single experiment multiplied by the time factor. This prolonged vasospasm causes cumulative injury, often irreversible, to the tissues.

These mechanisms operate in Raynaud's disease because it has been shown that the entire disturbance can be reversed by breaking the psychosomatic chain present in these patients. There is evidence that scleroderma is a more advanced manifestation of Raynaud's disease. This is based on the fact that in both diseases there is striking uniformity in the time relationship between the development of clinical manifestations and incidents in the life situation which are a threat to security. The intensity of this interaction is dependent upon a defect in personality. In the subject who is unable to integrate his problems fear stimulates the sympathetic pathways and thereby the smooth muscles of his minute vessels. If there is no resolution, chronic vasospasm persists.

The interplay of emotional forces and blood flow has been repeatedly observed in our clinic, and in many patients upon whom sympathectomy has been performed it has been found that progression of the process is not averted unless we can resolve the basic psychologic disturbance.

Dr. Heath: Turning now to management of peripheral vascular diseases, there are very few substances which have not been used in the therapy of organic peripheral vascular disease. None are very successful. On the other hand, the therapy of vasospasm is rational and usually highly effective. Procaine nerve block and preganglionic sympathectomy when well chosen are time-tested and proven procedures. Dr. Bridges will discuss them in some detail.

Dr. Bridges: Dilatation of the blood vessels of the arm and leg may be accomplished by inhibition of the vasoconstrictor activity of the sympathetic or autonomic nerves. The sympathetic outflow to the upper extremity leaves the spinal cord (as a portion of the anterior root) from the second thoracic segment to as low as the eighth thoracic segment. The outflow to the lower extremity is from the thoracolumbar cord, specifically lumbar through up to the fifth thoracic segment. From each of these anterior roots a white ramus communicantes passes to the corresponding sympathetic ganglia. The postganglionic connections are grey rami to the spinal nerve or to adjacent blood vessels or to the sympathetic trunk.

Accordingly, one may paralyze sympathetic activity by spinal anesthesia or by novocain infiltration into the extradural

[6] Foisie, P. S. Traumatic arterial vasospasm, *New England J. Med.*, 237, 295, 302, 1947.

space. In these instances the conduction of efferent vasoconstrictor impulses over the anterior roots is impaired, either intradurally or extradurally. If low spinal anesthesia is used, only the legs will show evidence of vasodilatation; if the anesthesia extends to the upper thoracic segments, the arm will also partake of this vasodilatation response.

Inhibition of vasoconstriction impulses to the arm or leg may be obtained by interruption of these impulses at one of two regions of the sympathetic chain itself. All of the impulses passing to the upper extremity reach the inferior cervical and first and second thoracic ganglia, and from these ganglia postganglionic fibers go to the major vessels or to the brachial plexus. Accordingly, novocain infiltration of the inferior cervical and first thoracic ganglia (so-called stellate ganglion) will release the vessels of the corresponding upper extremity of vasoconstrictor control. The lower extremity vessels will dilate when novocain is infiltrated about the third lumbar ganglia through which the preganglionic fibers intended for the lower extremity make their connection with the postganglionic fibers to vessels and the lumbosacral plexus. Distal to the sympathetic trunk the vasomotor nerves are too scattered to allow as complete inhibition of vasoconstriction although vasodilatation will follow division or novocain block of major peripheral nerves which carry a portion of the vasoconstrictor fibers through the extremity. The median and ulnar nerves are most commonly selected when one desires to produce vasodilatation in the hand by peripheral nerve block. The posterior tibial nerve is most readily blocked to cause vasodilatation in the foot.

In summary, there are three sites at which vasoconstrictor nerve fibers to the extremities may be blocked—the anterior roots by spinal anesthesia, the sympathetic trunk and the peripheral nerves. Of these sites the sympathetic trunk lends itself best to novocain block, alcohol block or surgical approach.

Novocain block of the sympathetic outflow to the upper or lower extremity is a relatively simple procedure which can be performed in the clinic. Stellate ganglion block will produce vasodilatation in the arm. About 5 cc. of 2 per cent novocain is deposited along the body of the first thoracic vertebra. The needle is inserted just above the clavicle within its medial third and directed inward, backward and slightly upward to strike the body of the first thoracic vertebra. The novocain diffuses readily in the paravertebral space so as to bathe the stellate and second thoracic ganglia.

Success in infiltrating the stellate ganglion is indicated by Horner's syndrome, that is, the production of a small pupil, lid drop and apparent enophthalmos on the side of the injected ganglion. The face will become dry and pink. The homolateral upper extremity will show in chronologic order dilatation of superficial veins of the hand and forearm, dryness of the skin of the entire upper extremity and lastly the hand and forearm will become pink and warm. In the presence of a non-obstructed, normal vascular supply the skin temperature rise will exceed 5°c. Generally fifteen to thirty minutes will elapse before the full effect of the parasympathetic novocain infiltration has developed.

In similar fashion vasodilatation in the lower extremity will appear after lumbar novocain sympathetic block. It is possible to produce a high degree of vasodilatation by injecting 5 cc. of 2 per cent novocain close to the third lumbar ganglion which lies opposite the anterolateral aspect of the body of the third lumbar vertebra. Because of the difficulty of accurately placing a needle tip at this point, either two or four needles are used; they are inserted opposite the first and third ganglia or the first, second, third and fourth ganglia. The needle insertion is started at a point on the skin 5 cm. lateral to the corresponding spinous process. The transverse process is located and the needle point then directed just above the process and in an inward and medial direction to strike the lumbar verte-

bral body. This will be encountered at a depth of two and one-half finger-breadths beyond the depth of the transverse process. The novocain solution is deposited as close to the vertebral body as possible. It will diffuse through the paravertebral areolar tissue along the lumbar sympathetic chain for a variable distance.

Evidence of a successful block in the lower extremity consists of dilated superficial veins, dry skin due to diminished sweat gland activity and a pink, warm foot and lower leg, appearing in this sequence. Evidence of increased blood flow or vasodilatation after a novocain block is found in the increased skin temperature and the reddish-pink color, in the dilated veins, and may be detected by plethysmographic observation, thermostromuhr readings and, more recently, by a heightened curve of radioactive sodium diffusion.

Novocain sympathetic blocks are used both as diagnostic and as therapeutic procedures. Regardless of the type of peripheral vascular disease if there is a rise of skin temperature of the digits of the involved extremity equal or greater than 3°C., one may anticipate improvement of the disease or abatement of symptoms following removal of vasoconstrictor control. This would warrant the use of repeated novocain blocks or of surgical interruption of the autonomic system. On occasion a novocain block may produce marked improvement in symptoms although the skin temperature increase equals only 1 or 2°C. Repeated novocain blocks are in order rather than surgical sympathectomy, at least until a number of such blocks has consistently yielded symptomatic improvement.

Surgical sympathectomy of the upper or lower extremity is not a formidable procedure. The mortality rate should approximate zero and morbidity due to the operation should be of less than ten days' duration.

In each instance preganglionic types of sympathectomy are indicated. Due to the technical difficulty of resecting the fourth and fifth lumbar sympathetic ganglia, lumbar sympathectomies have always been preganglionic sympathectomies. To denervate the foot and lower leg, the second and third, or upper three lumbar ganglia are resected through a flank or lateral abdominal, retroperitoneal approach.

The maximum rise in skin temperature will occur in the toes and foot. In the intact normal individual there is a temperature gradient from the thigh to the toes, the lowest temperature being that of the toes. After sympathectomy the gradient is largely lost and the temperature of the toes tends to equal that of the thigh. In the presence of marked occlusive vascular disease this gradient persists after sympathetic block or sympathectomy, as the rise of surface temperature is correlated with an increase in blood flow through the extremity.

Preganglionic thoracic sympathectomy to improve blood flow to the arm is carried out through a paravertebral incision with removal of a 2 inch segment of the medial end of the rib and its articulating transverse process. The third, or second and third ribs are so resected. The second and third thoracic roots are divided proximal to the dorsal root ganglia. The thoracic sympathetic chain is divided below the third thoracic ganglia. The sympathetic trunk between the stellate, second and third thoracic ganglia is carefully preserved, allowing preservation of the postganglionic connections from their ganglia to the brachial nerves and arteries thereby producing a preganglionic type of thoracic sympathectomy.

The reason for insisting upon preganglionic sympathectomy is that after total ganglionectomy or postganglionic sympathectomy the vessels become ten times more sensitive to circulating adrenalin which nullifies the effect of removing vasoconstrictor neural connections. After preganglionic sympathectomy the arteries are about three times as sensitive to circulating adrenalin, but this is more than compensated for by the removal of neural vasoconstrictor control.

DOCTOR: How permanent is the relief of vasospasm after sympathectomy? I have

heard that in a few years patients with Raynaud's disease, for example, may have a recurrence of their spasm due to increased sensitivity of the denervated smooth muscle to adrenalin.

DR. BRIDGES: The duration of vasodilatation following sympathectomy is unknown, and apparently variable. If the underlying disease is essentially occlusive, return of symptoms is almost certain. Raynaud's patients who have been seen in this Clinic after sympathectomy with symptoms, generally have symptoms related to non-sympathectomized regions. In many patients the impact of the vasospastic state remains limited to the sympathectomized area, and in these cases vasodilatation and relief of symptoms has persisted for two to five years. I know of no longer follow-up series than of five years' duration.

The relation of adrenalin sensitivity to return of symptoms has been suggested, but other factors may well be more significant as indicated by the observation of progressive symptoms in non-sympathectomized regions as well as in sympathectomized parts in a small group of progressive and ultimately fatal cases of Raynaud's disease.

DR. HEATH: Recently two new approaches to the therapy of vasospasm have appeared. At the University of Michigan the development and clinical application of the tetraethylammonium ion as an autonomic blocking agent has been reported.[7] Certain sympatholytic agents have also been introduced. Dr. Gilman will discuss these.

DR. ALFRED GILMAN: Interest in the possible contribution of drugs to the problems of peripheral vascular disease has been stimulated by recent studies of drugs capable of blocking the effects of sympathetic nerve impulses. The two most promising agents are the tetraethylammonium ion and dibenamine. Their pharmacologic actions and therapeutic potentialities can best be appreciated by discussing them against the background of the theory of chemical mediation of the nerve impulse.

In brief, this theory states that postganglionic autonomic nerves release at their endings chemical substances which stimulate the effector cells. Postganglionic sympathetic nerves, with a few exceptions, release sympathin, a substance which probably closely resembles epinephrine in chemical structure. Postganglionic parasympathetic nerves release acetylcholine. The term adrenergic and cholinergic nerves are employed to designate the chemical mediator. The theory of chemical mediation, although originally applied to account for the stimulation of autonomic effector cells by postganglionic autonomic nerves, has become much broader in scope. Thus, there is a large body of evidence to indicate that chemical mediators are involved in synaptic transmission in autonomic ganglia and at the junction between motor nerves and striate muscle. In both these instances the chemical mediator is acetylcholine. Thus, both sympathetic and parasympathetic preganglionic nerves and motor nerves to skeletal muscle may be termed cholinergic.

Although there has been considerable reluctance on the part of many neurophysiologists to accept completely the theory of chemical mediation, there is strong evidence in its favor. Moreover, it affords a reasonable interpretation for the action of drugs. Thus, autonomic blockade can be accomplished by chemical agents which prevent the chemical mediator from combining with the receptor substance of the effector cell. Atropine is an outstanding example of a drug which blocks the effects of acetylcholine released from postganglionic cholinergic nerves. Blocking agents are rather specific in their action. For example, atropine does not prevent the action of acetylcholine on striate muscle; this is accomplished, however, by the alkaloids of curare. The recent investigations of Acheson and co-workers have demonstrated that the tetraethylammonium ion establishes a blockade at autonomic ganglia. In other words,

[7] LYONS, R. H., ET AL. The effects of blockade of the autonomic ganglia in man with tetraethyl ammonium. *Am. J. M. Sc.*, 213: 315, 1947.

although acetylcholine is released at the terminations of the preganglionic fibers, in the presence of the tetraethylammonium ion the ganglion cell remains unaffected and no postganglionic impulse follows preganglionic stimulation.

The pharmacologic actions of the tetraethylammonium ion are those to be expected from a functional autonomic denervation at a ganglionic site affecting both adrenergic and cholinergic postganglionic nerves. For example, the pupil assumes a neutral position and no longer responds to light. Motor activity of the gastrointestinal tract is greatly decreased, micturition is impaired, etc. Pertinent to the present discussion is the fact that adrenergic vasoconstrictor fibers are blocked. Peripheral resistance is decreased and peripheral blood flow increased. Compensatory vasomoter reflexes are lost and postural hypotension develops. However, it is obvious that the therapeutic usefulness of the tetraethylammonium ion is limited because of the ubiquitous effects of a blocking agent acting at a ganglionic site. Furthermore, the drug is rapidly excreted and its effects are of relatively short duration.

Although there are numerous drugs effective in blocking postganglionic cholinergic nerve impulses, there is a dearth of agents capable of adrenergic blockade. Those available in the past have been nonspecific in their actions and have been much too toxic for therapeutic use. Interest in sympatholytic drugs has been greatly stimulated by the investigations of Nickerson and Goodman on the efficacy of dibenzylbetachloroethylamine (dibenamine) to block selectively the effects of epinephrine and adrenergic nerve stimulation. Not only is the compound capable of effecting a functional sympathetic denervation but the actions are long-lasting, being measured in periods of days. Furthermore, although the compound possesses toxic side actions, Hecht and Anderson have demonstrated that adrenergic blockade can be accomplished in humans. Again the pharmacologic actions can be anticipated if one keeps in mind that all of the known adrenolytic and sympatholytic drugs block only the excitatory and not the inhibitory effects of epinephrine and sympathetic nerve stimulation. Thus, there are no effects on the smooth muscle of the bowel and the bronchial tree. However, miosis occurs and the excitatory adrenergic impulses to the vascular bed are blocked. The vascular responses are similar to those elicited by the tetraethylammonium ion but in the case of dibenamine actual reversal may occur due to the fact that the inhibitory effect of epinephrine on blood vessels may be unmasked. For example, the blood pressure may fall in response to the injection of epinephrine. Similarly the cold pressor test or brief periods of anoxia may cause a fall rather than a rise in blood pressure.

The therapeutic applications of dibenamine are yet to be adequately defined. There is the real possibility that the toxic side actions of the compound may be greatly attenuated in one of its congeners. Surely this group of compounds will afford investigators in the field of vascular disease valued research tools and perhaps effective therapeutic agents.

DOCTOR: The reports on the therapeutic value of tetraethylammonium chloride in peripheral vascular diseases are conflicting. What are your views?

DR. HEATH: The use of the tetraethylammonium ion therapeutically has not produced satisfactory results. Two properties of the compound seem to be responsible for this. In the first place, the substance is rapidly excreted in the urine so that any effect is necessarily temporary. We have not observed prolonged remission of vasospasm even with repeated daily exhibition of the drug. This is contrary to other published results. Second, the effect of the substance is widespread upon all cholinergic synapses although the autonomic ganglia are most sensitive; therefore, selective vasodilatation cannot be obtained. This may be important in instances of occlusive disease in an extremity where generalized vasodilatation may result in an

actual decrease in available blood to the diseased area.

Sympathetic or adrenergic blocking agents such as the benzodioxanes, dibenamine (benzyl-β-chloroethylamine) and priscol (benzylimidazolines) certainly lack specificity and may present other objections to their use. In addition the benzodioxanes, for example, directly stimulate the smooth muscle of blood vessels while producing adrenergic (933 F) or both adrenergic and sympathetic (883 F) stimulation. Dibenamine blocks adrenergic effects on smooth muscle and does not directly stimulate the muscle but, as Dr. Gilman pointed out, is non-specific, long-acting and not an entirely benign substance. Priscol blocks adrenergic stimulation of smooth muscle and may dilate peripheral vessels directly but is uncertain in action and may have undesirable side effects.

At this clinic Dr. Mufson has been experimenting with the use of intra-arterial histamine and will briefly report on this method.

DR. ISIDORE MUFSON: An interesting aspect of therapy in peripheral vascular disease is the use of histamine in the relief of symptoms caused by obliterative endarteritis due to arteriosclerosis or angiitis. About two years ago we began to assay drug therapy of the peripheral vascular diseases by using radioactive sodium. We found that, as measured by the capacity to increase the diffusion rate of sodium, hypertonic saline and papaverine are practically inert whereas histamine by iontophoresis is a potent vasodilator. Histamine is not used by iontophoresis in endarteritis, however, because the insensitive skin of these patients is susceptible to electrical burns, but it can be given intravenously and so administered effectively reduces blood flow as judged by lowering of the radiosodium diffusion rate in the foot. It opens the healthy vessels of the upper half of the body at the expense of the diseased vessels of the legs. To fix histamine in the diseased arteries of the lower extremity histamine is given slowly by infusion from a "pressure bottle" into the femoral artery so that very little escapes into the general circulation.

As the histamine enters the femoral artery a definite erythema spreads over the thigh from the groin to the knee, becoming more intense as the treatment continues. The back of the leg, then the front and finally the foot become pink. The extent and degree of the effect is variable. Patterns appear in pink and white which suggest the location and degree of the arterial blocks. The pale areas soon may become suffused as collaterals dilate under the influence of histamine. If the infusion is given too rapidly, histamine may escape into the general circulation and then the head and neck become very red while the foot is mottled and dusky. When the speed of flow is reduced, the foot becomes pink as the face again pales. A rise in skin temperature follows the erythema rapidly in the thigh and more slowly in the leg and foot; many patients show an increase of 6°C. in their toes. An erythema may be present with very little rise in temperature. The presence of both erythema and a rise in temperature over the skin of the calf indicates an increase in blood flow in the calf muscles which was found to be a *sine qua non* for relief of pain in the calf.

Figure 1 demonstrates that the diffusion of radiosodium after infusion of histamine is always greater in the calf and less so in the foot. This is to be expected because the block is more severe and collaterals less available in the foot. The superficial veins of the leg invariably become distended.

These effects represent a cross section of the immediate responses noted in a group of twenty-eight patients with endarteritis obliterans who had been receiving weekly intra-arterial infusions of as much as 1 mg. of histamine base in 500 cc. normal saline. No other treatment was used concurrently and each patient had a backlog of one or more types of treatment from nine months to five years.

To evaluate the efficacy of intra-arterial histamine infusions the criteria chosen were

the effect on two symptoms of arterial insufficiency in the lower extremities: first, walking tolerance, the number of city blocks a patient is able to walk before he is forced to stop by a cramp in the calf; second, sleep tolerance, the number of hours in bed before the patient is awakened by a cramp in the calf which forces him out of bed for relief.

There were three types of response in walking tolerance. A very good group consisted of nineteen patients. These began with a walking tolerance of from one to three blocks; after a series of weekly infusions they were able to walk from fifteen to twenty blocks without stopping. They have maintained this improvement often without further treatment. The good group totaling six patients attained between six and ten blocks from a low of one to two blocks. Monthly treatments were given to maintain this level. In the poor group of three patients no improvement appeared after six treatments, when they were discontinued. Sleep tolerance was improved in 100 per cent. In less than two to six treatments patients who could barely rest slept through the night. They were our most grateful patients.

The oscillometric readings, which were very low (0 to 1 in all except one patient) remained unchanged, showing that the major block persisted. In spite of this the treatment had developed an efficient collateral circulation or at least had made it available. Why such a durable and competent collateral circulation should develop after this treatment is not altogether clear. Histamine is a potent vasodilator, at least as effective as sympathectomy by block or section in the presence of an obliterative endarteritis, as judged by production of erythema, rise in skin temperature and rise in radiosodium diffusion curve. We surmise that the direct effect of histamine does not last longer than six hours although the record of the results suggests that vasospasm has been permanently reversed. Analysis of the problem may give the reason. To begin with a primary force such as the degenerative process initiates a block in one or more arteries. The collaterals are available but cannot take over the burden because they are in reflex spasm as a result of the original block and its attendant distress. Some patients are helped by resting for six weeks or more because the collaterals open spontaneously. The patients whom we treated did not develop adequate collateral circulation spontaneously but apparently did so after administration of histamine.

Success in the treatment of patients with histamine rests not alone on the presence and availability of a competent collateral circulation but also on the absence of a cause for persistent reflex and histamine-resistant vasospasm of these same collaterals. It is advantageous to have a procedure which can be repeated as often as necessary to care for new problems as they arise, an advantage which sympathectomy does not possess.

SUMMARY

DR. HEATH: Our knowledge of the diseases of the peripheral blood vessels is small. Arteriosclerosis and thromboangiitis obliterans result from unknown causes so that definitive therapy is impossible. Somewhat more is known about the factors governing vasoconstrictor tone and vasospasm; in such conditions a mechanism is often discernible even though incompletely understood. Nevertheless, it is upon this knowledge that the investigative and therapeutic approach to the problems of peripheral vascular disease is largely based, and it is clear that by interrupting the sympathetic supply either spasm or the normal vasoconstrictor tone can be considerably decreased often to therapeutic advantage.

Blood flow through an extremity is extremely variable depending upon temperature, emotion, physical activity and other body functions. Extensive arteriovenous shunting which takes place in the hand and the foot adds to the magnitude of these changes. Whereas considerable information may be gained about the state of peripheral flow by inspection and palpation,

which may be placed into objective qualitative terms by the use of skin temperature determinations, oscillometry and arteriography, resort must be had to the venous occlusion plethysmograph for quantitative information. Recently the use of adrenalin iontophoresis of the skin has made it possible to make approximate measurements of blood flow to muscle. As yet no adequate method exists to measure peripheral blood flow during any state except rest.

Examples of vasospastic disorders improved by sympathetic procaine block or sympathectomy are given and a detailed description of these procedures is included in the clinic. It should be emphasized that careful evaluation of the probable effects of sympathectomy by the initial use of a procaine block should be carried out before an operative procedure is undertaken.

Use of autonomic blocking agents such as tetraethylammonium chloride is at present restricted to diagnostic procedures since their action is widespread and temporary. Sympatholytic agents so far available are too uncertain for general use. It is to be hoped, however, that further progress along these lines may result in a more practical application of these principles.

The intra-arterial use of histamine appears to have a sound physiologic basis and in the hands of Dr. Mufson seems to produce good results. This is particularly true of cases in which no appreciable spasm has been demonstrable by nerve block and in which the chief complaint is intermittent claudication. If further experience confirms these early results, a valuable therapeutic approach will be available for a group of patients heretofore considered beyond aid.

Clinico-pathologic Conference

Pneumococcal Meningitis*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, F. M., (B. H. No. 156274), was a forty-eight year old white married tool sharpener who entered the Barnes Hospital on February 27, 1948. He was comatose on admission and never regained consciousness; the following brief history was obtained from his wife. The family history and past history were, as far as could be determined, non-contributory. The patient had been in good health until two weeks before entry when he first noted a sense of fullness in his left ear and his hearing became less acute on that side. Eight days later he developed pain in the ear and a physician was called; he gave the patient one injection of penicillin intramuscularly and similar injections on each of the following four days. The patient was told that he had an ear infection which had spread to his blood. Two days before entry he complained of a severe headache which became progressively worse and necessitated sedation. A few hours previous to admission he suddenly became stuporous and delirious and was brought to the Barnes Hospital.

On entry to the hospital physical examination revealed a temperature of 39°C., pulse 80, respirations 32 and blood pressure 140/80. The patient was thrashing about in delirium and would not respond to questions. He appeared well developed but rather thin. The skin was hot and dry but no eruption was seen. There was no lymphadenopathy. The pupils were round, regular and equal and reacted well to light. The eyegrounds appeared normal except for slight narrowing of the arterioles. Examination of the left ear showed a small hematoma in the auditory canal. The drum was reddened, moderately scarred and retracted and the landmarks were not visible. The right ear was not remarkable. The nasal mucosa was red and dry and was covered with a small amount of mucopurulent discharge. The pharynx and tongue were likewise red and dry. Several of the teeth were carious. The neck was stiff; the neck veins were not distended and the trachea was in the midline. The thyroid could not be felt. Examination of the lungs revealed a few scattered ronchi bilaterally but no other abnormal findings. The heart was not enlarged; the rhythm was regular and the sounds were somewhat distant but there were no murmurs. Examination of the abdomen was negative. Neurologic examination revealed left divergent strabismus, although the external ocular muscles seemed intact, spasticity of all extremities, bilateral Babinski signs and questionable Kernig signs. A more detailed examination was not possible because of the patient's condition.

Admission laboratory findings were as follows: Blood count: red cells, 3,850,000; hemoglobin, 13 Gm.; white cells, 16,080; differential count: juvenile forms, 3 per cent; stab forms, 19 per cent; segmented forms, 68 per cent; lymphocytes, 15 per cent; monocytes 5 per cent. Urinalysis: albumin, 2+; sugar, 3+ (after intravenous glucose); acetone, 2+; sediment, occasional granular cast. Blood culture: negative.

Immediately after admission a lumbar puncture was performed. Manometric readings were not possible, but 10 cc. of cloudy

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fluid were withdrawn. The fluid was not xanthochromic; it contained 8,600 white cells per cu. ml. with acid, and of these 93 per cent were polymorphonuclear leukocytes. On smear extracellular gram-positive diplococci were seen; these proved on typing to be type VII pneumococci. Culture of the spinal fluid also revealed type VII pneumococci. At the time of the lumbar puncture 15,000 units of penicillin were introduced intrathecally. The patient was given 200,000 units of penicillin intramuscularly and subsequently received 100,000 units every two hours. He was also given 2 Gm. of sulfadiazine in 1/6 molar sodium lactate solution intravenously. He was seen by an otologic consultant who made a diagnosis of chronic left otitis media with possible brain abscess; he advised exploration of the mastoid cells as soon as the meningeal infection was better controlled. On the second hospital day a lumbar puncture was again performed and the spinal fluid was found to contain 20,000 white cells per cu. ml., of which 95 per cent were polymorphonuclear leukocytes. On smear, however, no organisms were seen and culture of the fluid was likewise negative. The patient's respirations became shallow and irregular and there were short periods of apnea. The breath sounds were almost inaudible. A bronchoscopy was performed but no evidence of bronchial obstruction was found. Soon thereafter there were convulsions localized to the left side of the face and these were followed by two generalized convulsions. Subsequently, intermittent twitching of the facial muscles was described. Roentgenograms of the sinuses and of the mastoid region showed no apparent abnormalities. A roentgenogram of the chest was not satisfactory.

On the second day the blood sulfadiazine level was 10.6 mg. per cent and the patient was given 4 Gm. of sodium sulfadiazine in 1/6 molar sodium lactate solution subcutaneously. After that infusion the sulfadiazine level rose to 13.2 mg. per cent. On the third hospital day the patient had a clonic convulsion which involved the left side of his body; it lasted approximately thirty seconds. Neurologic examination at that time showed a left hemiplegia with diminished reflexes. On a later examination, however, the reflexes were slightly hyperactive. The left pupil was noted to be smaller than the right and was fixed. The patient remained comatose.

After consultation by a neurologic surgeon the patient was transferred to the Neurosurgical Service and ventriculograms were done. The ventricular fluid was cloudy and contained large particles of exudate. Approximately 30 cc. of air were injected. X-ray films showed that the ventricles were dilated but there was no lateral shift. The third ventricle was normal except for dilatation. Following ventriculography, the patient developed severe epileptiform convulsions. He was given sedatives and placed in an oxygen tent and given parenteral fluids. His respirations, which had been irregular and shallow, improved. Another spinal puncture was performed but the fluid was so thick that it would not flow and it had to be aspirated. Approximately 40 cc. were withdrawn and 50,000 units of penicillin were injected into the subarachnoid space. Following this procedure, mild convulsions occurred. On the fourth day the left ventricle was tapped and air and blood-tinged cerebrospinal fluid were removed. The fluid was apparently not under pressure. Forty thousand units of penicillin were instilled. Another lumbar puncture was performed and 50 cc. of very cloudy fluid, filled with shreds of thick mucoid particles, were obtained. Irrigation was carried through the needle and 50,000 units of penicillin were injected. Simultaneously 50,000 units of penicillin were introduced into the right ventricle. The patient was obtunded and his respirations were of the Cheyne-Stokes type. Because of urinary incontinence, a retention catheter was inserted.

At this time another roentgenogram of the mastoids revealed the right to be normal but in the left there was increased density throughout the structure anterior to the

sinus plate. A large portion of the cell outline in that region could not be visualized and those cells which were seen were indistinct. A diagnosis of left mastoiditis was made. Following these studies, a left mastoidectomy was performed. The antrum was entered with a perforating burr and a small amount of pus escaped. The mastoid cells were extenterated. They appeared relatively normal except that the bone about the tegmental plate over the dura was somewhat soft; it came away easily exposing normal dura which did not bulge. The left lateral sinus was uncapped and appeared normal. The dura was removed back to the sinus which also appeared normal. The posterior mastoid sinus cells were normal. The incus was exposed but was left intact.

On the fourth day the temperature spiked to 41.8°c. from a level which had varied between 39 and 40°c. During the previous twenty-four hours the patient had received 100,000 units of penicillin intraventricularly, 100,000 units intrathecally and 800,000 units intramuscularly. He had likewise received 6 Gm. of sodium sulfadiazine, 1,000 cc. of lactate Ringer's solution, 2,000 cc. of ⅙ molar sodium lactate and 500 cc. of whole blood. On the fifth hospital day an attempt to enter the right ventricle was unsuccessful. The left ventricle was easily penetrated. Moderately bloody fluid was obtained which was not under pressure. Fifty thousand units of penicillin were instilled. A lumbar puncture was performed; the fluid at first had much exudate and was markedly cloudy. The cell count was 65,000; most of the cells were polymorphonuclear leukocytes. Fifty thousand units of penicillin were introduced. During the course of the day the patient had frequent brief convulsions during which he stopped breathing. His eyes were noted to turn to the left.

On the sixth hospital day painful stimuli elicited some response on the part of the patient. A lumbar puncture at this time revealed an initial pressure of 200 mm. of water and a final pressure of 150 mm. of water after removal of 25 cc. of fluid. The fluid appeared clearer and contained less sediment. The cell count was only 12,030. Later in the same day the patient had several more convulsions, each of which lasted about one minute. Although they were generalized, they were more marked on the left. Laboratory studies on the sixth day revealed the red count to be 3,210,000; hemoglobin, 13 Gm.; the white cell count was 8,800 with 35 per cent stab forms, 46 segmented forms and 19 per cent lymphocytes. The blood protein nitrogen was 21 mg. per cent and the blood sugar 114 mg. per cent. During this hospital stay the patient had repeated cultures of both ventricular and lumbar cerebrospinal fluid and all of these, except for the first one noted, were sterile. His temperature ranged between 39 and 40°c., except for occasional spikes. Shortly after one of his generalized convulsions on the sixth hospital day, March 4, 1948, the patient expired.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Dr. Bottom, would you care to comment on the x-ray films?

DR. DONALD S. BOTTOM: Films of the skull were attempted but only a lateral view could be taken and no remarkable findings were noted. Ventriculograms showed filling of both lateral ventricles and some air in the third ventricle. Although the ventricles were slightly dilated, they were in normal position and one would conclude that there was a block of the ventricular system distal to the third ventricle. The chest film was very poor but there was a suggestion of patchy infiltration throughout both lungs.

DR. ALEXANDER: This case is one of type VII pneumococcus infection of the leptomeninges and affords us an excellent occasion to discuss the modern methods of treatment of this disease. Before proceeding with the discussion of treatment, however, let us ask Dr. Harford to discuss this particular organism and tell us something of the route by which it may gain access to the meninges.

DR. CARL G. HARFORD: The type VII pneumococcus is one of the more common causes of pneumococcal pneumonia being responsible for approximately 6.5 per cent of all cases in a large series. It ranks next to types I, II, III and V in frequency of occurrence and is thus an important human pathogen. It is thought that infection due to the pneumococcus, whether it be pneumonia or meningitis, arises as a result of transmission of the organism from a carrier to a susceptible individual. Approximately 1 per cent of the population carries the type VII pneumococcus; this rate is rather low as is also the case with types I and II. One can postulate that when a patient develops an upper respiratory infection, perhaps due to a virus, secondary infection with the pneumococcus ensues. Probably in the case we are discussing the patient had a respiratory infection and then came in contact with an individual who carried type VII pneumococci. How he actually acquired the organism is a matter of conjecture although certainly inhalation of droplets, as a result of exposure to a cough or a sneeze, is quite possible.

DR. ALEXANDER: For how long are these organisms viable in dust? Could the patient have inhaled air-borne organisms?

DR. HARFORD: Yes, it has been shown that pneumococci are present in the dust of rooms in which carriers have been present.

DR. ALEXANDER: I believe certain studies have indicated that the organisms may persist for many days. This patient had apparent difficulties with his ear but when at operation the mastoid cells were exposed, they were not remarkably involved and when the dura was uncapped no important findings were observed. Do these data in any way invalidate the idea that the patient may have developed the meningitis via the middle ear?

DR. HARFORD: I do not think so. The pneumococcus has a reputation for passing into the central nervous system without leaving much evidence behind regarding its pathway. I think this patient certainly had something wrong with his ear and the chance of the ear having been the portal of entry seems to me to be excellent.

DR. ALEXANDER: By what other route may a patient acquire pneumococcal meningitis?

DR. HARFORD: Bacteremia arising in the course of lobar pneumonia may lead to meningitis.

DR. ALEXANDER: Would you comment on the relative incidence of pneumococcal and meningococcal meningitis?

DR. HARFORD: Meningococcus meningitis is more common during epidemic periods but in interepidemic periods the incidence of meningococcal and pneumococcal meningitis is about equal.

DR. W. BARRY WOOD, JR.: Sinus infection has not been mentioned as a portal of entry in pneumococcal meningitis. Would Dr. Harford comment on the incidence of pneumococcal meningitis following sinus infection?

DR. HARFORD: It certainly occurs but I cannot state the exact incidence.

DR. HENRY A. SCHROEDER: In regard to the rather unimpressive findings at the time of mastoidectomy it seems entirely conceivable that the intensive penicillin and sulfonamide therapy prior to operation had a definite effect on the infectious process so that when exploration was performed the findings were much less striking than they might have been originally.

DR. HARFORD: I think your point is very well taken.

DR. ALEXANDER: I would like Dr. Wood to discuss the problem of recovery from pneumococcal infections in general. Why is it, for example, that in untreated pneumococcal pneumonia the majority of patients recover whereas in untreated pneumococcal meningitis the mortality approaches 100 per cent?

DR. WOOD: I do not believe that your question can be answered completely, Dr. Alexander, but we may comment on some aspects of the problem. The anatomic structure of the lung is such that the defense mechanisms at that site, particularly those having to do with phagocytic cells, are

relatively efficient. It seems quite clear that the principal way in which the pneumococcus is destroyed in the body is by phagocytes, and the process of phagocytosis must therefore be studied if the mechanism of recovery is to be understood. The explanation for the efficiency with which phagocytes operate in the lung appears to relate to the tremendous surface area available to the leukocytes in this organ. The leukocytes utilize the extensive surfaces of the alveolar walls to destroy pneumococci by the mechanism of surface phagocytosis. When one contrasts the situation extant in the lung with that which obtains in an open cavity such as the pleural space or the subarachnoid space, it is apparent that the amount of surface available to the leukocytes is very small in the latter by comparison. Therefore the phagocytes in the meninges operate at a disadvantage since they have access to a relatively small area of tissue surface against which they can trap and thus phagocyte the encapsulated bacteria. As you have pointed out the case fatality rate when the pneumococcal infection involves the lung is relatively low, 20 to 30 per cent, whereas in the subarachnoid space it approaches 100 per cent.

DR. ALEXANDER: Is type specific antiserum given in an attempt to opsonize the organisms in pneumococcal meningitis?

DR. WOOD: Prior to the introduction of modern chemotherapeutic and antibiotic drugs, antiserum was the agent of choice in pneumococcal meningitis. When antibody is introduced into the subarachnoid space, the fatality rate is lowered somewhat but not to the degree that results from the use of penicillin. The antibacterial agents which stop the multiplication of the invading organisms are considerably more efficient than antiserum which does not affect multiplication but merely opsonizes the organisms and thus promotes phagocytosis.

DR. ALEXANDER: This patient received very large amounts of penicillin and although his general clinical condition progressively deteriorated and the spinal fluid cell count rose, all cultures were consistently negative except the initial one. What inference can be drawn from these findings, Dr. Hagemann?

DR. PAUL O. HAGEMANN: One can certainly postulate that the organism was quite susceptible to penicillin. Had it not been so I believe the organism would certainly have been recovered in subsequent cultures. I should like to ask whether penicillinase was used in the culture media. In view of the large amounts of penicillin which this patient received it is conceivable that enough penicillin was carried over into the culture medium to inhibit growth of the organism *in vitro*.

DR. HARFORD: We do not use penicillinase routinely in our laboratory although we do employ it when indicated. I am sorry that I cannot remember whether it was used in the cultures in this instance. It might be pointed out, however, that if enough penicillin was carried in the spinal fluid to the culture medium to inactivate the growth of the organisms *in vitro* then it would probably be sufficient to do so *in vivo*. It must be remembered also that penicillin not only exerts a bacteriostatic action but also under certain conditions it is bactericidal. For example, *in vitro* .06 or .07 units of penicillin will kill a rapidly growing culture of pneumococci in five hours. The amounts given this patient would result, in the blood at least, in exceedingly high levels many many times those necessary to kill the organisms *in vitro*.

DR. ALEXANDER: As a result of the pathologic changes due to the meningitis is it not possible that penicillin did not reach many of the organisms in this case?

DR. HARFORD: It is well known that penicillin, when administered parenterally, does not reach the subarachnoid space in high concentrations. That observation has led most authorities to recommend that penicillin be given intrathecally in meningitis. Even intrathecal penicillin may not be effective if there is thick plastic exudate in the meninges.

DR. ALEXANDER: At staff rounds several weeks ago we had an excellent discussion concerning the use of intrathecal penicillin participated in by the neurosurgeons, otolaryngologists, neurologists and internists. There seemed to be evidence both in favor and against the introduction of large amounts of penicillin directly into the subarachnoid space.

DR. HARFORD: Penicillin when given intrathecally to normal individuals causes chemical meningitis. When a patient already has meningitis, however, it is very difficult to know whether the penicillin increases the degree of meningeal irritation. Usually the chemical effect is ignored in favor of active treatment of the infection.

DR. ALEXANDER: It would seem well to raise the question, in the case under discussion, as to whether the patient was cured by the original 15,000 units of penicillin which were introduced at the time of the first lumbar puncture and if so whether his subsequent unsatisfactory course could have been either partly or completely due to the large amount of penicillin subsequently given.

DR. WOOD: The problem raised is a most difficult one. As you have stated, Dr. Alexander, we have discussed it at great length with the neurologists and neurosurgeons and there is much difference of opinion. The neurosurgeons have had a great deal of experience in treating advanced cases of pneumococcal meningitis. Patients such as this one, admitted to the hospital after having been treated inadequately, do not respond to the usual therapeutic regimen and are then sent to the neurosurgical service for more heroic measures. Dr. Henry Schwartz has given a large number of these patients repeated doses of 50 or even 100,000 units intrathecally or intraventricularly. On the other hand, most internists, pediatricians and neurologists hesitate to use more than 20,000 units a day because of the irritative action of the drug itself. The pathology of this case should be extremely instructive and I am very anxious to hear Dr. Dammin's findings. There would appear to me to be three possibilities: First, it is possible that we did not control the meningitis due to the fact that there was so much exudate over the surface of the brain that the organisms in the fibrinous exudate were unaffected by the drug. Second, the infection may have been controlled by penicillin but the inflammatory reaction in the meninges may have progressed to the point where it caused mechanical block of the foramina of Luschka and Magendie. Third, it is conceivable that the penicillin itself produced a continual meningitis. If viable organisms were found at autopsy, the neurosurgeon's point of view will be supported, namely, that very large doses of penicillin should be given. If the persistent meningitis appears to be of chemical origin, then a more conservative approach will seem indicated.

DR. ALEXANDER: Dr. Bottom, do you believe that the ventriculograms are indicative of internal hydrocephalus?

DR. BOTTOM: The ventricles are not as dilated as one usually sees, but the findings suggest some delay in absorption of cerebrospinal fluid.

DR. JOHN R. SMITH: Dr. Wood, would you comment further on the possibility which you previously outlined, namely, that the inflammatory reaction persisted after the pneumococci were destroyed.

DR. WOOD: When there is a severe inflammatory reaction to infection, there is often a long period during which the inflammation persists after the infection has been brought under control. This phenomenon is most often seen in the lung where x-ray shadows of a pneumonic lesion may become larger after the crisis, indicating a lag in the clearing of the exudate. Thus, the continuation of the inflammatory response, despite the fact that the organisms have been killed, indicates that all the sources of irritation have not been removed. The death of the organisms and the release of toxic products of the many bacterial cells act to prolong the inflammation. If there were a large number of organisms in the sub-

arachnoid space in the present case and they were all killed, there might still be enough of a stimulus to cause the inflammatory response to persist for some time. However, the response apparently continued for four days after the cultures had become negative and this period would appear to one to be too long for such a mechanism to operate. I believe that the two most likely possibilities are that there was either persistent infection or that the continued meningitis was due to the penicillin.

DR. HENRY H. GRAHAM: I do not know the findings which Dr. Dammin will describe, but investigators studying this problem have found that they can produce a reaction with penicillin that is indistinguishable from infection as far as the fibrous reaction in the meninges is concerned. Thus, in this case, it may be impossible to make a distinction.

DR. ALEXANDER: May the reaction give rise to a polymorphonuclear exudate?

DR. GRAHAM: Yes.

DR. WOOD: I should like to comment further on the fibrin reaction. The deposition of fibrin constitutes a part of the host's mechanism of defense against infection, but the process may in the end be harmful. In this case a fibrinous exudate will probably be disclosed over the surface of the brain, particularly at the base. The same type of reaction occurs in the pleural space in empyema. Until the present time we have had no satisfactory method of attacking this problem and patients die or are disabled because of the purely mechanical effects of the organized fibrin. Recently at New York University Dr. Tillett has obtained in relatively pure form from hemolytic streptococci a fibrinolysin which he injects into the pleural space to destroy fibrin after it has been laid down as the result of an experimental infection. Whether his observations in experimental animals will lead to a practical form of therapy remains to be seen, but his findings are already of the greatest interest. The patient under discussion today was one in whom the injection of a fibrinolytic agent into the subarachnoid space to remove the fibrinous exudate might have been most helpful.

DR. ALEXANDER: Is the fibrinolysin specific for fibrin arising from any form of infection?

DR. WOOD: Streptococcal fibrinolysin will lyse fibrin of human blood regardless of the process that caused it to arise.

DR. ROBERT J. GLASER: The streptococcal fibrinolysin may be further defined. Beta-hemolytic streptococci produce an enzyme called streptokinase which activates a fibrinolytic system within the blood; that is, the enzymatic product of the streptococcus does not in itself lyse fibrin but activates a lytic agent that is present in normal serum.

DR. HAGEMANN: In my opinion this patient probably had persistent localized meningitis. He had infection with inadequate therapy for four days before coming to the hospital. Such an interval constitutes a very long time when one is dealing with pneumococcal meningitis. The neurologic signs were rather localized. He had chiefly left-sided manifestations which I interpret as arising from meningitis adjacent to the left mastoid. I think it would be unlikely for penicillin to give rise to a localized reaction.

DR. HARFORD: One further point should be made. It seems to me that the actual cell count in the spinal fluid may not be a satisfactory indication of the condition of the patient. It not infrequently happens that when the first lumbar puncture is performed, the fluid is turbid as a result of the large number of bacteria present. The following day when the culture may have become negative and the bacteria are gone the cell count may rise considerably as a result of the process already referred to by Dr. Wood.

DR. GRAHAM: Under even inadequate penicillin therapy the cell count may not return to normal but it usually decreases and the patient's symptoms often clear. He may even become ambulatory for a matter of days or even weeks, only subsequently to have a focus in the brain that has not

cleared completely reactivate the meningitis. Therefore, in this particular infection apparent clinical cure does not always indicate permanent freedom from difficulty.

DR. ALEXANDER: In summary, it seems clear that this patient had pneumococcal meningitis which prior to his admission to this hospital had progressed to a point where irreversible changes had developed. He received very large amounts of penicillin parenterally and into the cerebrospinal fluid itself, and it is possible that although the infection was eradicated the inflammatory process resulting from either the meningitis or from penicillin itself may have led to such a severe reaction as to cause death. The tragedy of a case such as this lies in the fact that had this patient been treated promptly and intensively on the first or even the second day of his illness he would undoubtedly have been cured of the infection.

Clinical Diagnoses: Pneumococcal meningitis, ? controlled; ? multiple abscesses in the meninges and brain; ? meningitis due to irritation (by penicillin).

PATHOLOGIC DISCUSSION

DR. ALFRED DECKER: External examination revealed a well developed, well nourished, white male appearing about his stated age of forty-eight. The body weighed 65 Kg. The head was shaved. There were bilateral surgical incisions in the parieto-occipital regions. There was a partially sutured surgical incision anterior to the upper portion of the left ear from which two rubber-dam drains and a rubber tube extruded. The left ear canal was packed with a wick which was blood-stained. There were numerous needle punctures in all extremities and over the lower lumbar spine. When the body was opened, there were 300 cc. of turbid fluid containing a few flecks of fibrin in the abdominal cavity. There was no apparent serosal reaction. There were 200 cc. of faintly turbid fluid in the right pleural cavity, 100 cc. of similar fluid in the left and 50 cc. of clear fluid in the pericardial sac. Both lobes of the left lung were fixed by firm fibrous adhesions. The lungs weighed 1,350 Gm. and the dependent third of both lower lobes was dark red in color and nodular to palpation. There was no fresh fibrin on the pleural surfaces. On section the trachea and bronchi were seen to be filled with a white mucopurulent exudate. There were patchy areas in both lower lobes which presented the raised granular appearance of bronchopneumonia. The liver weighed 1,670 Gm., was dark red in color and on section revealed prominence of the central areas of the lobules. The right kidney weighed 190 Gm., the left 230 Gm.; both were dark and striations were dark colored and prominent. The other thoracic and abdominal viscera appeared grossly normal.

After removal of the brain examination of the dural sinuses revealed small thrombi, perhaps 7 mm. in their greatest diameter, in the posterior superior portions of both cavernous sinuses. These were loosely adherent, gray-pink in color and suggestive of antemortem thrombi. The dura over the left petrous ridge was slightly discolored. It was intact, however, and there was only minimal roughening of the cerebral surface. When the dura was stripped from this area, an operative defect was seen unroofing the mastoid air cells. This defect was filled with a firm hematoma without evidence of suppuration or bony involvement. In the left middle ear there was a drop of purulent fluid. The right petrous bone revealed extreme pneumatization with actual perforations of the bone subdurally but no evidence of inflammation in either the mastoid air cells or the middle ear. Examination of the brain revealed mucoid, yellow-white purulent material in the subarachnoid space over both cerebral hemispheres with concentration in the sulci and markedly predominant over the right frontal and parietal lobes. At the base of the brain there was similar exudate extending from the optic chiasm to the medulla and laterally over the anterior border of both cerebellar hemispheres. The areas of the foramina of Luschka bilaterally were matted

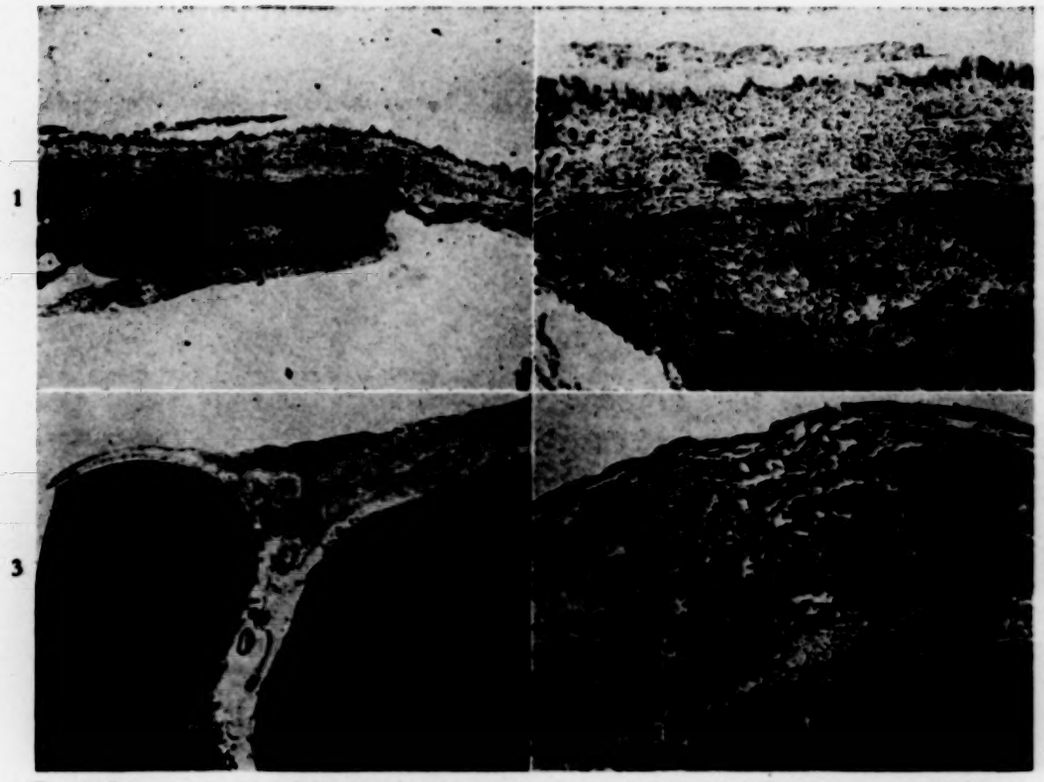


FIG. 1. Low power view of the dura from the mastoid area showing the inflammatory reaction on the cerebral surface.
FIG. 2. Another section of the area shown in Figure 1 under higher magnification. There is condensation of fibrin with much nuclear débris.
FIG. 3. Section from the right parietal area showing the dense collection of exudate.
FIG. 4. Higher power view of the section in Figure 3. Very few of the polymorphonuclear leukocytes are well preserved.

with thick yellow pus. Examination of the meningeal covering of the cistern revealed opacity but no frank exudate. Section of the brain revealed very slight dilatation of the ventricles and blunting of their outline with possibly 5 cc. of clotted blood in each. No exudate was demonstrable. The tracts of the ventricular punctures revealed considerable hemorrhage. Examination of the spinal cord revealed exudate over the dorsal aspect of the cord in the subarachnoid space from the cauda equina up to the mid-dorsal region. Cultures were made at the heart's blood, from the exudate over the cerebrum, and from the right lower lobe of the lung.

DR. GUSTAVE J. DAMMIN: We are dealing with a rather unique case which concerned not only the internist but also the neurologist, neurosurgeon and the otorhinolaryngologist. We have evidence that the patient had acute seropurulent otitis media on the left with acute purulent mastoiditis, as reported by Dr. Walsh in his operative note, an area of pachymengitis over the mastoid area and diffuse leptomeningitis more localized over the right cerebral hemisphere. There was no evidence of brain abscess or any other well circumscribed focus of infection. By gross examination we cannot accurately estimate the duration of these lesions and the duration of each lesion will influence our speculation regarding the sequence of events.

The lesion over the mastoid involved a small area. Figure 1 shows a low power view of the dura from the mastoid area with an inflammatory reaction on the cerebral surface. The peripheral portion consists of a loosely constructed fibrin reticulum and the cells within it are well preserved, but if one examines the deeper portion under higher power (Fig. 2), one finds a condensation

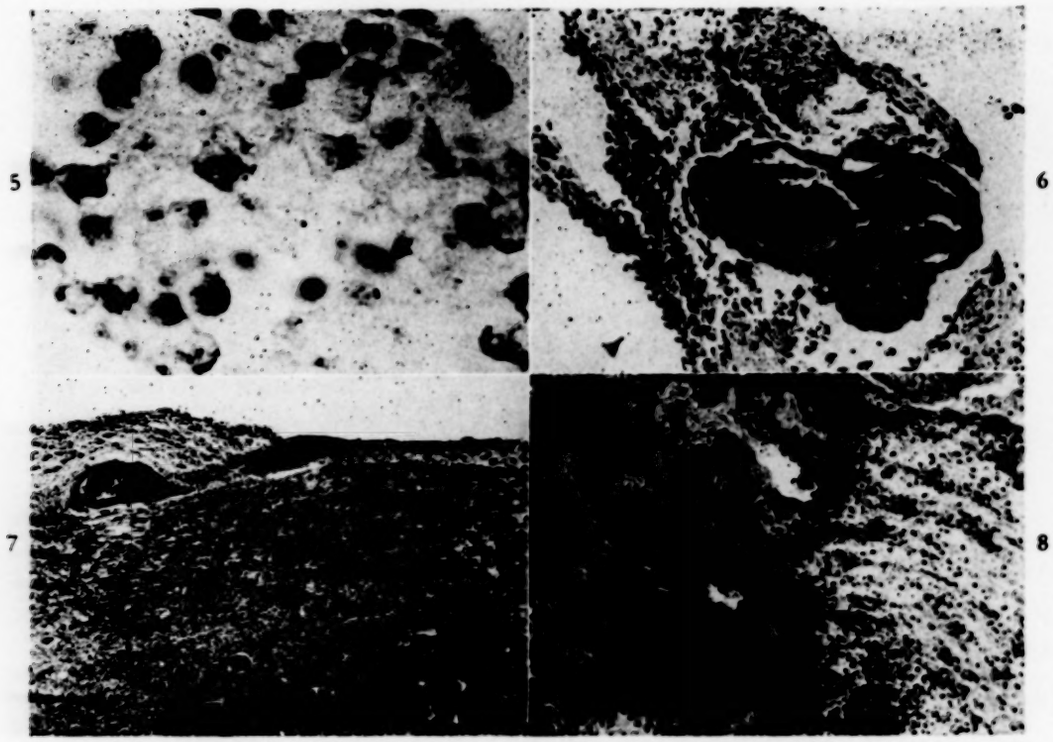
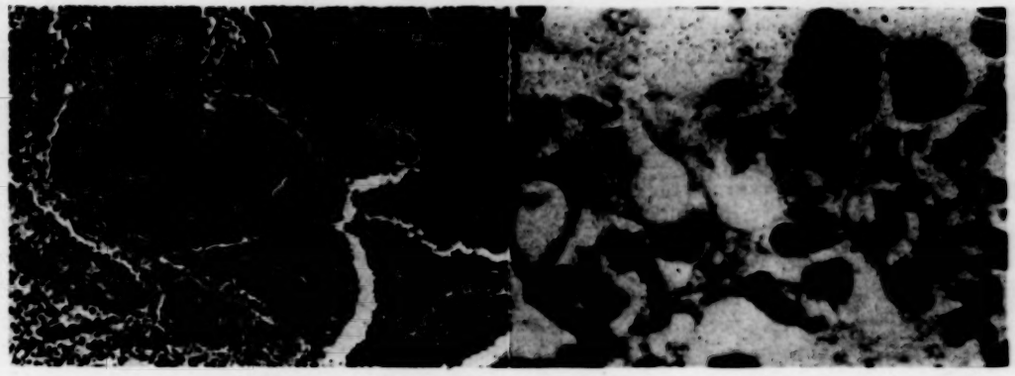


FIG. 5. Section of the exudate over the right parietal lobe showing organisms which morphologically resemble pneumococci.
FIG. 6. A section of the choroid plexus to show the inflammatory reaction.
FIG. 7. Section showing perivascular collection of cells adjacent to the ventricles.
FIG. 8. Section of one of the thrombi removed from the cavernous sinus. Note the presence of platelet columns.

of fibrin with much nuclear débris, suggesting a process at least several days old. The patient was operated upon on March 2nd and died on March 4th. The deeper portion of the process appeared to be more than two days old. I believe we can assume that it represented one of the early steps in the sequence of events which led to leptomeningitis. Bacteriologic stains revealed no bacteria to be present. In a section from the right parietal area (Fig. 3) note the width of the subarachnoid space and the dense collection of exudate which contains numerous degenerated leukocytes. Under higher power (Fig. 4) very few polymorphonuclear leukocytes in this portion are observed to show any degree of preservation. There were a few mononuclear cells found in some portions of the exudate. According to Walker and Johnson[1] who have studied the reaction to penicillin in the lumbar subarachnoid space, this reaction for some reason does not resemble the usual acute inflammatory reaction, in that it contains a relatively large percentage of lymphocytes. In none of the sections studied have we noted any great number of lymphocytes. In Figure 5 one sees organisms morphologically resembling pneumococci in the exudate over the right parietal lobe. They were difficult to find, only one being found in every six to ten oil immersion fields. The diplococci observed had the usual morphology; they were not swollen and did not appear to show any of the abnormal forms which penicillin occasionally induces *in vitro* and *in vivo*. Organisms were also found in the subarachnoid exudate over the cerebrum, cerebellum and spinal cord.

Grossly we found no evidence of ependymitis. When ventricular puncture was done, it was recorded that the fluid was thick and difficult to remove. It therefore

[1] WALKER, A. E., and JOHNSON, H. C. Principles and practice of penicillin therapy in diseases of the nervous system. *Ann. Surg.*, 122: 1125, 1945.



9 10

FIG. 9. A section of the lung showing early pneumonia.
FIG. 10. Section of the lung stained for bacteria. Note the presence of both cocci and bacilli.

surprised the neurosurgeons when, at autopsy, the ependyma was found to show little if any reaction. The only evidence remaining that there was any reaction in the ventricular system was found microscopically in the choroid plexus where there was a mild inflammatory reaction. (Fig. 6.) We searched the ependyma looking for a reaction in order to explain the purulent fluid reported by the neurosurgeons. The ependymal lining was normal but there were perivascular collections of cells found adjacent to the ventricles; (Fig. 7) they constitute evidence that there was an inflammatory process involving the ependyma, or at least the wall of the ventricular system. Figure 8 is a section of one of the thrombi, described by Dr. Decker, removed from the cavernous sinus. It contains platelt columns and we have no reason to doubt that it represented an antemortem thrombus, probably of very short duration, which probably appeared within the last two or three days of life; it contained no bacteria.

Figure 9 shows a section from the lung taken at the point of confluence of several bronchioles. The bronchioles and adjacent alveoli contain fibrin and well preserved polymorphonuclear leukocytes. Apparently this process again is one of recent origin. A bacterial stain (Fig. 10) showed gram-positive diplococci and bacilli staining in the manner in which gram-negative bacilli stain with the Goodpasture method. In other fields we found cocci and rods that we identified as gram-negative. Cultures taken at autopsy from the heart's blood on media containing both para-aminobenzoic acid and penicillinase and cultured both aerobically and anaeorbically for three weeks showed no growth. Material taken from the meninges was cultured and a heavy innoculum used. Dr. Beamer reported finding six colonies of Staphylococcus aureus and one colony of a coliform organism. He was not inclined to place significance on these findings. On culture the left lower lobe of the lung showed Aeorbacter aerogenes, hemolytic Staph. aureus and alpha-hemolytic streptococci.

From what we have seen grossly and microscopically we may speculate as to the sequence of the lesions. Initially there was an otitis media. The first section showed the pachymeningitis of several days' duration. It was localized but not circumscribed. Probably the leptomeningitis followed the pachymeningitis. If we had not found the localized pachymeningitis, we could not have been too much disturbed because there are many pathways by which the infection can travel from the middle ear to the central nervous system. In this case we suspect that the pachymeningitis represented the point of entrance of the infection from the middle ear into the central nervous system. As you recall the x-ray films of the mastoid were read as negative. That finding does not rule out an area of mastoiditis which had as yet not led to destruction of air cells when it was controlled by drug

therapy. I am inclined, however, to believe that the mastoid was involved rather late, probably more recently than the dura mater, on the basis of Dr. Walsh's finding pus but no destruction of air cells; again, we do not know to what extent and for what duration the penicillin may have kept the mastoiditis circumscribed.

It is difficult to account for the purulent fluid in the ventricles. We have no evidence of ependymitis; there was some exudate on the choroid plexus and an inflammatory process within the plexus.

The dilatation of the ventricular system indicates the presence of at least a partial obstruction to the flow of cerebrospinal fluid from the ventricles into the subarachnoid space. This degree of obstruction must have been dependent upon several factors, namely, the presence of thick, purulent exudate at the lateral foramina, the increased production of cerebrospinal fluid which occurs in bacterial infections of the central nervous system and the presence of purulent exudate in the cerebral and spinal subarachnoid spaces.

Regarding the left hemiplegia and convulsions which appeared first only on the left and then became generalized, it is a common observation in children that when meningitis complicates either a mastoid or middle ear infection, convulsions or paralysis occur on the side of the ear involved. It is believed that exudate may gravitate and in the case under discussion the exudate as was described by Dr. Decker was much more prominent over the right parietal lobe. Figure 4, which showed the exudate over that lobe, was not of a magnification high enough to show the degenerative changes in the ganglion cells with satellitosis and neuronophagia. It is likely that these changes were the result of increased pressure in the subarachnoid space and the ventricular system.

Pneumococcal meningitis is notorious for the residual lesions which may persist after maximum therapeutic effect from drugs has been achieved. Such a sequence of events is particularly common in children. In a report by Hutchins and Davies[2] of fifteen cases in incidence of children under two years of age treated with intrathecal as well as intramuscular penicillin there were nine recoveries and yet five of these patients showed severe enough permanent central nervous system damage that they required prolonged institutional care. Sweet and his co-workers,[3] reported sixteen cases of pneumococcal meningitis with seven recoveries. Of the seven patients who recovered, two were children and both of these showed marked mental deterioration following treatment. In this case and possibly in other cases the effect on the cerebrum may be due to the pressure of subarachnoidal exudate and to intraventricular pressure. Judging from the distribution of the exudate and its character, one might speculate as to whether the immediate treatment of pneumococcal meningitis should not be the introduction of penicillin directly into the cisterna rather than into the lumbar subarachnoid space. Walker and Johnson introduced 20 to 30 thousand units of penicillin into the lumbar subarachnoid space and were unable to recover any of the drug in cisternal fluid. On the other hand, when penicillin is introduced directly into the cisterna, there is good diffusion throughout the subarachnoid space and the ventricular system; indeed, the diffusion is better than when penicillin is introduced directly into the ventricles. Walker and Johnson further noted that when a normal monkey was given a large dose of penicillin intravenously, only a very minute amount appeared in the spinal fluid. If, on the other hand, sterile meningeal irritation was produced, levels of penicillin in the spinal fluid rose to between 10 and 50 per cent of the blood level. Such levels would lie in the therapeutic range and it seems fair to assume that in meningitis there is increased permeability of the blood brain barrier so that penicillin is able to reach the spinal

[2] Hutchins, G. and Davies, J. A. V. Penicillin treatment of pneumococcus meningitis in infants. *J. Pediat.*, 27: 505, 1945.

[3] Sweet, L. K., et al. Treatment of pneumococcic meningitis with penicillin. *J. A. M. A.*, 137: 263, 1945.

fluid in significant concentration. These points are important when one is faced with treating an infection which, even if present for a short length of time, may lead to lesions that are difficult to reach with penicillin. Therefore, once the diagnosis of penumococcal meningitis is made, particularly if the patient has been seen early in the course of the disease, it would seem that massive intravenous doses may produce satisfactory spinal fluid levels, but if this result is not achieved then direct introduction of the antibacterial agent into the cisterna or even into the ventricles seems justified.

The pneumonia which was described in this patient was probably of short duration and one might estimate from the appearance of the fibrin and leukocytes that it had been present for only two to three days. The recovery of bacteria from the lesion in the lung suggests that the organisms perhaps were penicillin-resistant since the patient had had massive doses of parenteral penicillin. If indeed they were penicillin-resistant, streptomycin may have been indicated.

In summary, we attribute the inflammatory reaction to the infectious process. We base this conclusion on the absence of lymphocytes and the presence of bacteria which show no morphologic alteration and therefore may possibly have been viable. It is conceivable that the infectious process represented a small focus which was not reached by the antibiotic. As far as the differentiation of penicillin toxicity and infection insofar as parenchymal changes are concerned we are not able to make a definitive statement in answer to that problem. We think that the changes in the cerebrum could have been produced by the large amount of exudate and the increase in intraventricular pressure. However, it is fair to point out that in monkeys large doses of penicillin intrathecally have led to cerebral damage, convulsions and even death.

Anatomic Diagnoses: Acute seropurulent otitis media, left; focal subdural purulent pachymeningitis involving mastoid area, left; (history of acute mastoiditis, left; mastoidectomy, left, two days); acute purulent leptomeningitis involving the cerebrum, more marked on the right, base of the brain, cerebellum and spinal cord; exudate in the ventricular system; (history of antemortem isolation of pneumococcus type VII); dilatation of the lateral and third ventricles, slight; thrombus in the posterior superior third of each cavernous sinus; bronchopneumonia of the lower lobes, moderate.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Reports

Simmonds' Disease*

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SINCE Morris Simmonds first noted that marked pathologic changes in the adenohypophysis were associated with generalized cachexia, there have been numerous reports confirming this. In the review article of Escamilla and Lisser in 1942[1] a total of 101 typical clinical cases with pathologic verification were collected from the literature. Since then many other cases have been reported.[3–24]

By far the most frequent cause of pituitary cachexia is post partum necrosis of the pituitary gland.[1,2] Our first case is a typical example of such a pathologic process. Another important cause of this syndrome is a neoplastic process involving the pituitary gland. Our second case is that of a chromophobe adenoma of the pituitary gland which was surgically extirpated leading to the train of symptoms and signs of pituitary cachexia.

CASE REPORTS

CASE 1. F. T., a twenty-five year old colored female, was transferred from another hospital to the Goldwater Memorial Hospital on June 18, 1946. Her family and past history revealed that her mother had been treated for lues at the age of nineteen. At the age of twelve the patient was also treated for lues with a course of alternating hip and arm injections over a period of one year. In 1934 she had epistaxis and migratory pain, heat and swelling of nearly all her joints of about six weeks' duration. A diagnosis of rheumatic fever was made. The swelling subsided but soreness and stiffness persisted in these joints; this was aggravated by damp weather. The patient knew of no associated heart involvement.

Her illness began in June, 1943 shortly after she was delivered of a seven month stillbirth. She was admitted to the hospital with fever, dyspnea, chest pain and signs of pneumonia at the right base of the lung. Marked anemia was present. The temperature gradually fell after therapy with fluids, digitalis and blood. There was a transitory albuminuria. She was discharged after thirty-eight days with a diagnosis of lobar pneumonia, anemia and rheumatic heart disease. In October, 1943 she became pregnant for a second time and in the seventh month was again hospitalized because of a blood pressure of 200/120, albuminuria and edema of the lower extremities. On admission the patient's urine showed 1 plus albumin, 30 to 40 white blood cells per high power field and 10 to 15 red blood cells per high power field. She was also anemic. With rest and a low salt diet, her arterial pressure fell to 156/85 and the edema diminished. On May 16, 1944, five days after admission, the patient spontaneously delivered a living seven month male. The delivery was complicated by a retained placenta and copious hemorrhage. Two days post partum abdominal examination revealed tenderness in both lower quadrants. She also developed dyspnea and signs of consolidation in the lower lobe of the right lung. Hemoptysis was present and a diagnosis of pulmonary embolism was entertained. The white blood count at this time was 26,900. Penicillin was administered intramuscularly. On the fourth post partum day she had a transfusion followed by a severe reaction and a fever of 106°F. The following day a purulent discharge from the vagina was noted and her temperature was 103.6°F. The patient was treated vigorously with penicillin and fluids. The clinical diagnosis at the time was a post partum septicemia secondary to thrombophlebitis of the pelvic veins. After a very septic and stormy period she improved gradually

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and left the hospital about twenty-seven days after admission.

Following her discharge from the hospital, the patient began to complain of progressive weakness and anorexia. She lost 50 pounds of weight in three years. Her menses did not reappear and she noted a gradual loss of pubic and axillary hair. In April, 1946, about two years after her previous hospitalization, she developed a fever and because of increasing weakness and joint pains was admitted to the hospital. There she was described as an emaciated colored female. The blood pressure was 75/50. The heart was normal. The blood chemistries were essentially normal but the glucose tolerance curve was flat. She had a marked hypochromic anemia. During her hospital stay the fever and joint pains subsided with salicylate therapy.

On her initial physical examination at Goldwater Memorial Hospital the findings were as follows: Normal temperature, pulse and respirations; blood pressure 70/50 and weight 63½ pounds. She was small, poorly developed and cachectic. There was alopecia of the scalp and loss of axillary and pubic hair. The conjunctivae were pale. The gingival margins were spongy and friable and there was pallor of the oral mucous membranes and lips. The chest was thin and there was atrophy of the muscles of the pectoral girdle and of the breasts. A systolic blow was heard over the fourth intercostal space just to the left of the sternum, not accompanied by a thrill. The abdominal viscera were not palpable. Atrophy of all muscles of the extremities was present. There was some limitation of motion of elbow and finger joints. On pelvic examination the cervix felt small and atrophic and was adherent along the left vaginal wall. The vagina was very shallow. Speculum examination showed an infantile cervix.

The hemoglobin content of the blood was 8 Gm. per cent, the red blood count 3,100,000, the white blood count 6,900 with 72 per cent neutrophile polymorphonuclear leukocytes, 19 per cent lymphocytes, 7 per cent monocytes and 2 per cent eosinophile leukocytes. The corrected sedimentation rate was 41 mm./hr., with a hematocrit of 23 per cent. The Wassermann and Kline tests were negative. Kidney function was markedly reduced as evidenced by elevated blood urea, low urea clearance, diminished phenolsulfonphthalein excretion and inability to concentrate urine. The fasting blood sugars ranged from 65 to 68 mg. per cent. The creatinine was 0.7 mg. per cent and the uric acid 3.7 mg. per cent in the blood. The blood calcium, phosphorus and phosphatase were all normal. The total cholesterol was 160 mg. per cent with 83 mg. per cent esters. The total proteins were 7.1 Gm. per cent, the albumin 2.1 Gm. per cent and the globulin 5 Gm. per cent. The chlorides ranged from 630 to 715 mg. per cent. The bromsulfalein and cephalin flocculation tests were negative. The undiluted prothrombin time was 19.2 (normal 15) seconds and the dilute 61.3 (normal 40 to 42) seconds. Gastric analysis showed no free hydrochloric acid after histamine. A glucose tolerance curve showed an increased tolerance. Bone marrow, platelet count, red blood cell fragility and reticulocyte counts were all normal. The basal metabolic rates ranged from −21 to −36.

X-ray examination of the skull and all bones was negative. Chest x-rays showed accentuation of the left middle cardiac segment. The ECG showed a low T_1, diphasic T_2 and inverted T_3 and T_{CF_4}.

The patient's course at Goldwater Memorial Hospital was rapidly downhill. Frequent episodes of epistaxis and bleeding from the gums were controlled with difficulty. The prolonged prothrombin time returned to normal with vitamin K therapy very slowly but shortly thereafter rose to abnormal levels again. She had many purulent skin infections which responded to penicillin. Treatment with adrenal cortical extract and later desoxycorticosterone acetate and thyroid extract did not result in improvement. About six weeks after admission a blood transfusion was followed by chills and fever. Two weeks later she developed enlargement of the submaxillary nodes and left parotitis, with a rise in temperature to 101°F. and lymphocytosis. Although penicillin controlled this acute infection, the white blood count remained elevated from 8,000 to 17,000 with a lymphocyte count of 50 to 70 per cent. The patient had another severe transfusion reaction in September, 1946. At that time an effort was made to increase her caloric intake by intravenous and tube feedings. Simultaneously, there was a recurrence of bleeding from her nose and gums. Attempts to correct an elevated prothrombin time by means of vitamin K therapy were not successful. The patient's condition became steadily worse. The severity of her anemia increased markedly despite therapy. The blood pressure fell to 66/38. Prior to her death the

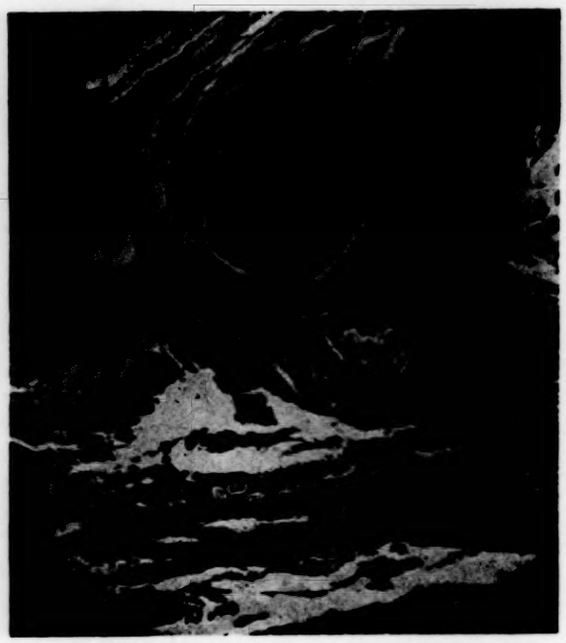

FIG. 1. Case 1. Fibrosis of the anterior lobe of the pituitary gland which surrounds the posterior lobe. Only scattered cells of the former remain (× 25).

blood urea nitrogen rose to 112.8 mg. per cent. She lapsed into shock and expired on October 24, 1946, about four months after admission.

Postmortem examination revealed the following: Grossly, the body was that of a poorly developed and markedly emaciated female negro. The brain weighed 915 Gm. It appeared small and pale. There were no gross abnormalities. The sella turcica was somewhat small but appeared to be within normal limits. The pituitary, however, was markedly decreased in size and the various parts of the organ could not be differentiated. It appeared more uniform than normal and fibrotic. Several small hemorrhagic areas were found on the inferior surface.

A small amount of amber fluid was found in the right pleural cavity. Both lungs showed congestion and mottled areas of infiltration. The heart was smaller than normal and weighed 275 Gm. The pericardial cavity was completely obliterated but otherwise the heart was normal. The liver weighed 760 Gm. and appeared pale and atrophic. On section it was homogeneous and pale yellow in color. Many small petechial hemorrhages were noticed throughout the parenchyma. Both kidneys were markedly reduced in size. The right kidney weighed 75 Gm. and the left 55 Gm. The capsules stripped with ease revealing a mottled brownish surface, showing many petechial hemorrhages. The pelves and ureters appeared normal. The uterus was small in size and firm in consistency. The ovaries were small and atrophic. The thyroid was normal in size, shape and consistency. The parathyroids appeared normal. The adrenals showed beginning autolysis. The cortices, however, appeared to be of normal thickness.

Microscopic examination revealed the following: The capsule of the pituitary gland was markedly thickened due to fibrous tissue deposition. This was mostly acellular and in areas appeared to be hyalinized. The anterior lobe was markedly atrophic and fibrotic. Its exact delimitations were indefinite due to the merging of its connective tissue with that of the capsule. It was markedly shrunken in size and contained only small regions of cells. Some pseudoacinar formation was found, the cells being small with darkly-staining nuclei and faint translucent cytoplasm, apparently chromophobe cells. No definite basophilic or eosinophilic elements were noted. The fibrotic anterior lobe partly surrounded the posterior lobe. A few irregular spaces containing colloid material were seen in the region between the anterior and posterior lobes. The intermediate lobe was not clearly visualized. The posterior lobe was compressed but otherwise showed no marked abnormalities. (Fig. 1.)

The pericardium was thickened due to deposition of collagen. There was no evidence of rheumatic heart disease.

The capsule of the liver was not thickened. The sinusoids were congested and there was considerable atrophy of the central portions of the lobules. Many of the periportal spaces were widened and contained large collections of lymphocytes and histiocytes together with occasional polymorphonuclear cells. There was also an increase of fibrous tissue in these areas. The pancreas appeared normal except for patchy areas of fibrous tissue. Most of the glomeruli of the kidneys were altered. The capillary loops were decreased in number and showed marked fibrosis. The tubules varied somewhat in size and many of them contained red cells and hemoglobin casts. There was moderate lymphocytic infiltration of the interstitial tissue.

The periphery of the ovary was made up of cellular interlacing fibers. There were a few primordial follicles, some of which appeared to be undergoing degeneration. The central portion of the ovary was made up of collagenous

fibers, many fibroblasts, small thick-walled blood vessels and several corpora albicantes. The smooth muscle bundles of the uterus appeared normal throughout. There were many small and moderately-sized, thick-walled vessels, some of which showed complete occlusion. There was no normal endometrial lining noted.

The capsule of the adrenals appeared thickened, the cortex and medulla normal. The acini of the thyroid gland varied somewhat in size and shape but all appeared normal. They were filled with colloid which stained with the same degree of intensity. The acini were lined by low cuboidal cells.

The skeletal muscle generally was normal except for small areas where the muscle was replaced by hyalinized fibrous tissue. In these areas, there was a slight perivascular infiltration by round cells and fibroblasts. The follicles of the lymph nodes were large and irregular. The sinuses were dilated and showed a marked increase in reticulum cells and fibrous tissue.

Final Diagnoses: Atrophy and fibrosis of pituitary, apparently due to old infarction; chronic adhesive pericarditis; pericholangitis; perisplenitis; lymphoid hyperplasia of spleen; chronic glomerulonephritis; cortical atrophy of adrenals; fibrosis and atrophy of ovaries; atrophy of uterine endometrium; lymphoid hyperplasia of lymph nodes; hypochromic anemia; lobular pneumonia; pulmonary edema; cachexia.

Case II. A. S., a thirty-eight year old single white man, was admitted to Goldwater Memorial Hospital on December 19, 1940, with the major complaints of visual disturbances of ten years' duration, weight loss and wasting and abdominal cramps of five years' duration.

The patient had been well until 1930 except for occasional attacks of severe headaches. He then had, for the first time, symptoms of left temporal hemianopsia. This persisted without any objective progression of visual impairment. In December, 1934 he began to have severe, constant, predominantly left frontal and occasionally nuchal headaches lasting for a month. The headaches then became milder but still were constant and were localized mostly over the left frontal region. He had been unable to have penile erections since the summer of 1934. In January, 1935 he experienced a sudden recrudescence of bouts of headaches, accompanied by vomiting. He was drowsy and gave a delayed response to questioning and was incontinent of urine and feces. From that time on his gait became slow and unsteady.

He was admitted to a hospital with these complaints in February, 1935. On admission he weighed 130 pounds, was well developed and in no acute distress. He had slight bitemporal pallor of the optic disks and marked bilateral temporal visual field defects. A diagnosis of craniopharyngioma was made. X-rays of the skull showed erosion of the sella turcica which appeared to be twice the normal size. On March 14, 1935, a tumor 2 cm. in diameter, bulging from the sella turcica, was partially removed by suction and curettement. In April, 1935 the patient was reoperated upon and the tumor was removed, "leaving the floor of the fossa smooth and glistening." It was found to impinge on both optic nerves and the optic chiasm. The pathologic specimens measured together about 15 by 17 by 10 mm. Microscopically, they showed fibroblastic proliferation with diffuse lymphocytic infiltration and a large amount of normal pituitary tissue. After a stormy postoperative course the patient was discharged to the out-patient department. In June, 1935 he was rehospitalized for abdominal cramps and vomiting. He slept a great deal, yawned frequently, was mentally dull and had a delayed response to questioning. He had bilateral anosmia and the optic disks were white. He was weak and there was spasticity of both arms and legs. All deep tendon reflexes were diminished and the ankle reflexes absent. In August, 1935 he weighed 102 pounds, looked cachectic and had marked hypersensitivity to cold. His skin was dry and cold, and there was marked loss of subcutaneous tissue. He walked with a stoop.

In April, 1937 he was transferred to another hospital where his blood pressure was 100/68; scarce pubic and axillary hair were noted at this time. His abdomen was distended and extremely sensitive to pressure which elicited muscular and visceral cramps. He was treated with vitamin C, antuitrin, sodium chloride, desiccated thyroid gland and whole pituitary gland without results. There he developed painful swollen joints which resembled those of rheumatoid arthritis. X-rays of the bones showed marked decalcification.

In December, 1940 he was transferred to Goldwater Memorial Hospital. His appearance was sallow and simulated that of a little old woman. Pubic and axillary hair were absent.

His blood pressure was 120/80. Both pupils were round and equal but reacted poorly to light. He had horizontal nystagmus and both optic disks were pale. The left arm and leg were fixed in extension, the right leg in flexion. He had a right clawhand deformity. The joints were painful. There was a deformity of the fingers of the left hand with displacement of bones at the interphalangeal joints. The right foot showed a hoof deformity and the ankle was painful and swollen. All his muscles were atrophied. He weighed 70 pounds. A tourniquet test showed many petechiae below the occluded area. There was no change in the x-rays of the skull from that noted previously. During his various hospitalizations his red blood cell count was 3,800,000 to 3,900,000, the hemoglobin varied from 72 to 80 per cent. Among the abnormal laboratory findings were the following: the fasting blood sugar varied from 48 to 82 mg. per cent. A sugar tolerance curve was flat, the highest value being 97 mg. per cent one hour after ingestion of glucose. An insulin tolerance test was performed with 10 units of regular insulin resulting in a drop of blood sugar to 17.5 mg. per cent. The patient remained in insulin shock for twenty-four hours despite vigorous therapy; he recovered gradually. Just before death the serum sodium level was 124.7 mEq./L. and the serum chlorides 105 mEq./L. The serum calcium ranged from 9.4 mg. per cent to 12 mg. per cent and the phosphorus from 2.6 to 3.8 mg. per cent. The total cholesterol ranged from 246 to 138 mg. per cent with variations in the ester contents of from a trace to 200 mg. per cent. The basal metabolic rate varied between −16 and −28. The blood Wassermann reaction was negative.

During the patient's stay at Goldwater Memorial Hospital he had several severe infections of the skin of his feet and several bouts of vomiting, at one time bringing up guaiac-positive material. He also had an acute parotitis. Otherwise, his general condition remained stationary. He was well oriented, able to speak slowly and to read with moderate difficulty. He had frequent episodes of abdominal cramps. His blood pressure levels fell to 86/60 during the last year before death. In April, 1947 he was transferred to another hospital for endocrine therapy. Two weeks after admission there he suddenly went into pulmonary edema and expired.

Postmortem examination revealed the following: Grossly, the body was that of an old wizened man, weighing approximately 55 pounds and measuring 4 feet 3 inches in height. There were marked deformities of the extremities. All muscles showed advanced atrophy. The penis was infantile and only the right testicle was found in the scrotum.

The cerebral hemispheres were approximately symmetrical. The gyri were flattened and the sulci narrowed throughout. There was a large lobulated, encapsulated tumor mass over the ventral midline of the brain which was firm, rubbery and gray. There were two main lobes of the neoplasm. The lower and more posterior part was the portion which lay within the sella turcica. It was enclosed in a dense opaque grayish-white membrane. There was a constriction between it and the lobe lying dorsal and anterior to it. This was the point of junction of the extra- and intrasellar portion of the tumor through an orifice in the diaphragm of the sella turcica. The intrasellar portion of the tumor measured roughly 3 cm. transversely, 2 cm. dorsoventrally and 13.4 cm. anteroposteriorly. The suprasellar portion of the tumor, which could not be separated easily from the overlying hypothalamus and leptomeninges, was the larger segment and measured roughly 3.5 cm. dorsoventrally, 23.4 cm. from side to side and 2.5 cm. anteroposteriorly. The right optic nerve had been displaced posteriorly and laterally for a considerable distance. Its posterior displacement was roughly 1.5 cm. It was reduced to two-thirds of its normal size. It was difficult to identify the left optic nerve but a flattened band of tissue to the left of the suprasellar portion of the tumor may have been this structure. The chiasm was attenuated to a narrow ribbon. Mid-sagittal section of the brain revealed intense compression of the hypothalamic region with invasion of the floor of the third ventricle. The interventricular foramina were partially occluded by the neoplasm. The aqueduct of Sylvius and fourth ventricle were of normal size. (Fig. 2.)

Both lungs seemed well aerated. From their dark red cut surface frothy pink fluid could be expressed. The heart was smaller than normal. The pericardium and myocardium seemed grossly normal. There was a gray nodular thickening of the free edges of the mitral cusps and slight shortening of the chordae tendinae. The liver was small, weighing 710 Gm. but otherwise appeared normal. The spleen weighed

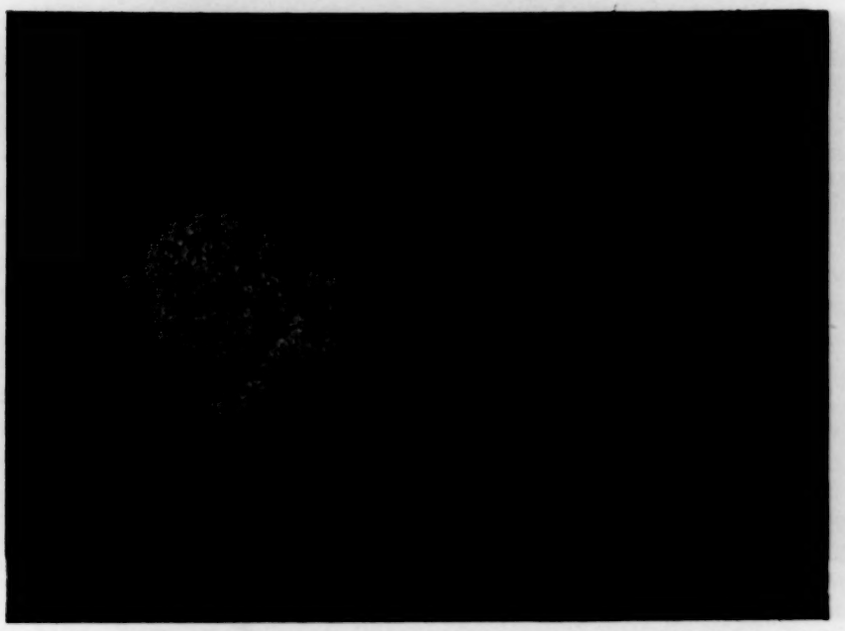

FIG. 2. Case II. Tumor of the pituitary region involving the base of the brain which has compressed the third ventricle and extended to the lateral ventricles.

45 Gm. and showed grossly a moderate increase in fibrous tissue with indistinct malpighian corpuscules. The cardiac end of the stomach showed an atrophic and thin mucosa. The small and large intestines were normal. There was a horseshoe-shaped single kidney with the open end superiorly weighing 150 Gm. The ureters arose from the lower medial portion of each side. On section the kidney appeared normal. The adrenals measured 2.5 by 2.5 by 0.2 cm. each and appeared grossly normal. The testicles were small. The thyroid gland weighed 4.6 Gm. and was rather small and firm. The parathyroids did not appear grossly abnormal.

Microscopic examination revealed the following: The intracranial tumor had a high cellular and richly vascular structure. The tumor cells were polygonal and had a moderate amount of finely granular cytoplasm. Their nuclei were uniform, oval, spherical and showed no mitosis. The cells were arranged in rows and columns about the capillaries in a regular pattern. A diagnosis of chromophobe adenoma of the pituitary gland was made. (Fig. 3.)

Sections through the heart were essentially normal except for the mitral valve which was somewhat thickened but showed no increase of cells or blood vessels. Lung sections revealed marked congestion. Some areas showed emphysema and patches of central fibrosis.

The capsule of the kidney appeared thickened. The cortex showed patches of inflammatory cells, mostly lymphocytes. Small deposits of calcified material were seen in a few tubules. Some glomeruli were completely or partly hyalinized. The renal medulla showed a moderate amount of interstitial fibrosis. Occasional slight increase of cells in the periportal spaces of the liver were seen.

The adrenals appeared atrophic, especially the cortex which in some regions was limited to four to five rows of cells. The reticular layer appeared to be the most involved. The capsule

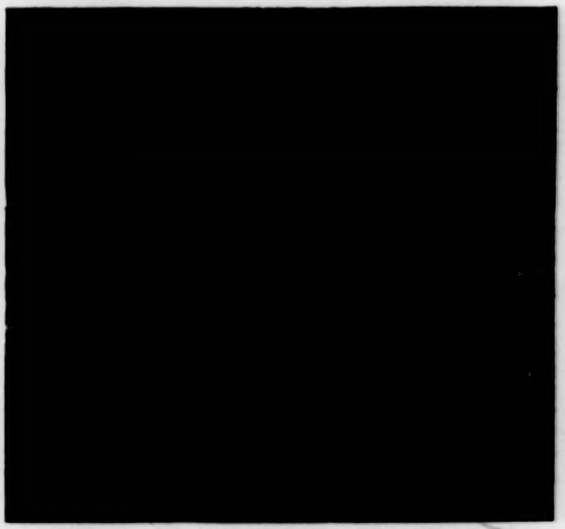

FIG. 3. Case II. Neoplastic growth of the pituitary gland consisting of cells with dark nuclei and pale cytoplasm characteristic of chromophobe cells (× 400).

of the gland appeared somewhat thickened. The tubules of the testes appeared shrunken and consisted of loose fibrous structure in which few cells were found. The capsule of the thyroid gland was moderately thickened. The acini were generally small and lined by flattened cuboidal cells. Some contained colloid material which stained unevenly; others were atrophic and contained no colloid. A considerable amount of connective tissue, hyaline and calcified material was found between the alveoli. There was slight fibrosis of the parathyroid glands.

Section through bone marrow showed an increase in erythroblastic elements. The megakaryocytes were normal in number.

Final Diagnoses: Chromophobe adenoma of pituitary; emphysema and congestion of lung; horseshoe kidney; chronic arthritis; atrophy of adrenals, testes, thyroid and skeletal muscles; fibrosis of parathyroids; cachexia.

COMMENTS

The course of Case 1 is comparable with that of the cases with Simmonds' disease due to post partum necrosis as described by Sheehan.[2] The disease dated from the delivery which was complicated by post partum retention of the placenta, hemorrhage and puerperal sepsis. All the clinical features described by Escamilla and Lisser and by Sheehan[1,2] were present: emaciation, absence of pubic and axillary hair, amenorrhea, loss of libido, hypotension, dry skin and atrophy of breasts and genitalia. In addition, the following laboratory findings confirmative of the diagnosis were present: low basal metabolic rate, low fasting blood sugars, high glucose tolerance, anemia and gastric anacidity.

An unusual finding toward the termination of the patient's course was the presence of lymphadenopathy with marked lymphocytosis and diminution in polymorphonuclear leukocytes in the peripheral blood. Bone marrow aspiration during life showed normal cellular elements. Dougherty and White[26,27] have made observations which suggest that the regulation of circulating lymphocytes is under control of the anterior pituitary gland, mediated by the adrenal gland. They also pointed out that an elevated lymphocyte count and hyperplasia of the lymphoid tissue has been recorded in Addison's disease. Selye[28] linked the endocrine and lymphatic systems in the so-called "alarm reaction." De la Balze and his co-workers[29] further suggested that there is an increase in lymphocytes and a relative decrease in neutrophiles in both panhypopituitarism and Addison's disease and that the increased sensitivity to infections is due to a failure to release immune globulin from tissue. The frequent infections and the hematologic picture are in accord with the hypothesis of these investigators.

The postmortem findings were characteristic of Simmonds' disease except for the presence of a grossly and microscopically normal thyroid gland in spite of the low basal metabolic rate. In Sheehan's report about one-third of the thyroid glands studied showed normal appearance or slight atrophy only. One might conjecture that the low basal metabolic rates were a result of prolonged malnutrition.

The interest in the second case lay in the fact that the patient was a completely apituitary man since 1935 when all the contents of the sella were removed. Postmortem observation in 1947 failed to reveal the presence of any normal pituitary tissue. The patient apparently had symptoms referable to a deficiency of the anterior lobe only. Marked hypotension, visceral cramps and low blood sodium pointed to adrenal cortical insufficiency. At necropsy there was marked atrophy of the adrenal cortex.

The relationship of chronic arthritis and bizarre deformities of the extremities to his apituitarism is difficult to evaluate. We have been unable to find another case report in which this type of arthritis has complicated the course of Simmonds' disease. It has been suggested by some observers[30] that "hypoactivity of the pituitary may lead to increased susceptibility to infection, anemia, fatigue and generalized atrophy, conditions common in atrophic arthritis." This patient had many severe infections of the skin, parotid gland and lungs as did the first

patient. However, lymphocytosis was not found in the peripheral blood of the second patient.

SUMMARY

1. Two cases of hypopituitarism with different etiologies are described with necropsy findings.

2. The first case was typical of post partum necrosis of the pituitary and on necropsy showed atrophy of all endocrine glands with the exception of the thyroid. Lymphocytosis and lymphadenopathy were noted as a late feature. The literature on this relationship is reviewed.

3. The second case was an apituitary individual following surgical extirpation of a chromophobe adenoma. Bizarre arthritis was an unusual complicating feature.

Acknowledgments: We are greatly indebted to Professor H. L. Sheehan of the University of Liverpool for having reviewed our first case and its microscopic slides and to Dr. J. Murray Steele, Director of the Third Medical Division of Goldwater Memorial Hospital, for his suggestions in the preparation of this paper. We are also indebted to Dr. Abner Wolf who reviewed the gross and microscopic findings of the brain in the second case.

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Friedländer Bacillus Meningitis Successfully Treated with Streptomycin*

Consideration of Friedländer Bacillus Infections in Diabetes

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The purpose of this article is (1) to present the report of a case of Friedländer bacillus meningitis successfully treated with streptomycin† and (2) to record the significant frequency of diabetes among patients who have had Friedländer bacillus infections. The latter point, made conspicuous by our patient who had extreme hyperglycemia and glycosuria during the acute phase of her illness, has been further emphasized by a careful review of the literature relating to Friedländer bacillus infections, both of pulmonary and extrapulmonary types, in connection with the presence or absence of evidence of diabetes in the published articles.

Meningitis due to the Friedländer bacillus is a relatively rare disease and is well recognized as a highly fatal one. Prior to the sulfonamides the mortality of the disease exceeded 99 per cent, and many cases undoubtedly did not reach publication largely because they differed in no important way from those already reported. In recent years, however, chemotherapy has resulted in several cures and the syndrome has assumed new interest in medical journals.

In 1943 Ransmeier and Major[1] reported a case of Friedländer bacillus meningitis unsuccessfully treated with sulfanilamide, and in their review of the subject listed twenty-nine additional cases which had been reported up to that time. Of this group of thirty cases only three survived, one following mastoid drainage and two treated with sulfapyridine. It was estimated by Ransmeier and Major that in the large cities of the United States the Friedländer bacillus was responsible for three cases of meningitis in 3,714. In their analysis they indicated that most patients with childhood cases were seen under the age of nine months, that the years between three and twenty were surprisingly spared and that the infection appeared to show an unusual predilection for older adults and the aged.

Since the above report, three further cases of Friedländer bacillus meningitis have reached publication. In 1943 Mori[2] reported the infection in a twenty-six month old infant successfully treated with a sulfonamide (soluseptazine). During the same year Macky and Morris,[3] reporting from New Zealand, described a fatal case of Friedländer bacillus meningitis following prostatectomy for prostatic abscess. The infection in the third case, reported by Tartakoff, Grynbaum and LeCompte[4] in 1946, followed craniotomy for brain tumor. The patient was treated with streptomycin and although he died suddenly of pulmonary embolism, the postmortem findings were suggestive of healing meningitis and the authors believed that the antibiotic had probably been successful in controlling the infection.

† The streptomycin was provided by the National Research Council from supplies assigned for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents. The Pfizer product, Lot No. 466, was used.

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The case of Friedländer bacillus meningitis reported in this paper represents to our knowledge the first clearly defined streptomycin cure to appear and the thirty-fourth case to be reviewed in the literature.

CASE REPORT

The patient, a forty-eight year old colored female, was admitted to the Third Medical Division of Bellevue Hospital on April 11, 1946, in a comatose state. The history, which was elicited from friends and later substantiated by the patient, revealed that she had been suffering from an infection of the right middle ear for over three months, and that myringotomy had been performed at least twice with a drainage of pus. Her complaints had been few, however, until four days prior to admission when earache reappeared and was accompanied by headache. Myringotomy was again performed and the patient received three intramuscular injections of penicillin. Her complaints did not subside and two days prior to admission chemotherapy was changed to sulfadiazine, the patient receiving a total of 18 Gm. of the drug over a thirty-hour interval. Approximately twenty hours before admission the patient became feverish, thirsty and confused and she noticed an increased urinary output. After a period of irrational behavior she lapsed into coma. The past history was entirely negative except for a small amount of weight lost during the previous year. Although an aunt had diabetes, the patient had no personal knowledge of the disease in herself.

At the time of admission the temperature was 102°F., pulse rate, 136; respiratory rate, 38 and blood pressure, 145/75. The patient was a well developed and nourished comatose negress who was hyperpneic with an odor of acetone to her breath. Hirsutism of the chest and chin was present. The right ear drum was angry red and bulging, and the scar of a recent myringotomy stab was noted but without drainage. The left ear was normal and funduscopy showed no abnormalities. The remainder of the physical examination was normal except for the presence of characteristic meningitic signs with nuchal rigidity and positive Kernig and Brudzinski signs.

The blood count at this time revealed 20,000 white cells; 4,200,000 red cells and 12 Gm. hemoglobin. Spinal tap yielded a cloudy fluid which contained 7,500 white cells, 75 per cent of which were polymorphonuclears. Of this fluid the protein measured 360 mg. per cent, sugar 286 and chlorides 660. The culture was positive for Friedländer bacilli which did not type with antisera A or B. Urinalysis showed 4 plus glucose and 3 plus acetone. The blood sugar was 445 mg. per cent.

The patient responded favorably to therapy for diabetic ketosis with infusions of 5 per cent glucose in saline and half-hourly intramuscular injections of regular insulin. Since the spinal fluid culture report was not available immediately and the smear failed to show organisms, she received combined chemotherapy with 20,000 units penicillin intrathecally at least once daily, 30,000 units intramuscularly every three hours and sulfadiazine both intravenously and by stomach tube. The dosage may be seen on the accompanying illustration. By the third hospital day the urine had cleared of acetone but showed a consistent 4 plus reaction for glucose in spite of 70 to 100 units insulin daily. Her temperature remained over 102°F., leukocytosis persisted, the spinal fluid remained purulent and the clinical condition remained critical. She was transferred to the Ear, Nose and Throat Service and modified radical mastoidectomy was performed under local anesthesia; the mastoid cortex was removed and much pus was drained from the bone, a drain being left in the wound. For the next three days, however, spinal taps continued to yield purulent fluid. On the sixth hospital day the temperature was over 103°F., white blood count was 17,500 with 75 per cent neutrophiles and glycosuria continued at 4 plus in spite of administration of 150 units insulin daily, given intramuscularly at four-hour intervals with protein and carbohydrate feedings by a stomach tube. In spite of the administration of both penicillin and sulfadiazine, bacteriologic studies of samples of spinal fluid obtained on the first, fifth and sixth hospital days, and also of the mastoid drainage at the time of surgery on the third day, revealed the presence of Friedländer bacilli.

On the sixth day streptomycin therapy was instituted with 0.4 Gm. intramuscularly every four hours and 0.1 Gm. diluted in 10 cc. distilled water intrathecally once daily. Sulfadiazine was continued orally but penicillin was discontinued. Intrathecal therapy was continued for six days to a total of 0.6 Gm. and intramuscular therapy for eight days to 16.8 Gm.; the total by both

routes was 17.4 Gm. At the termination of streptomycin therapy, sulfadiazine was also discontinued; the total amount of the drug used over a twelve-day interval was 68 Gm.

During the first forty-eight hours of streptomycin therapy a marked clinical improvement was observed and the patient began to feed herself by mouth. By the second week the insulin requirement fell from 150 to 25 units daily, and on the twenty-fourth day she was finally regulated with 10 units protamine-zinc-insulin daily. During streptomycin therapy there was a gradual drop in temperature, but it never fell below 100°F. until the third week. On several occasions the intrathecal administration seemed to be causally followed by rises in temperature. Cultures of the spinal fluid, however, were sterile at the time of tapping twenty hours following the first intrathecal dose and remained sterile thereafter. After an early rise in the white count of the peripheral blood to 20,800 it fell to 13,000 during therapy and thereafter returned to normal levels. The temperature remained normal after the eighteenth day, and by the forty-ninth day, at which time the patient was ambulatory about the ward, the surgical mastoid wound had completely healed.

During convalescence a glucose tolerance test yielded a curve of diabetic character with a rise in blood sugar to 308 mg. per cent after 100 Gm. of glucose by mouth and a sustained hyperglycemia for the usual three-hour period. Spinal fluid cleared in its gross appearance and protein, sugar and chloride levels returned to normal. However, the fall in the cell count was slow. On the sixty-second hospital day, forty-nine days after streptomycin had been discontinued, 33 lymphocytes/mm.^{3} were still present. At this time the patient was entirely symptom-free; physical and neurologic examinations showed no abnormality other than diminution of auditory acuity on the right and some hyperesthesia of the right forehead, orbit and cornea. She was discharged on June 12th and during the next three months she gained weight, attended the diabetes clinic and was maintained on 10 units protamine-zinc-insulin daily.

On September 18th, three months following discharge, the patient was requested to re-enter the hospital for re-evaluation and she did so although enjoying excellent health at the time. She was afebrile and the physical examination was normal. Other than for 1 to 2 plus glycosuria, urinalysis and blood count showed no abnormality. A lumbar puncture yielded a clear cerebrospinal fluid under normal pressure and containing no cells. Other laboratory findings on this fluid were: protein 66 mg. per cent, sugar 83, chloride 750. In view of the fact that her protracted fever while in the hospital sug-

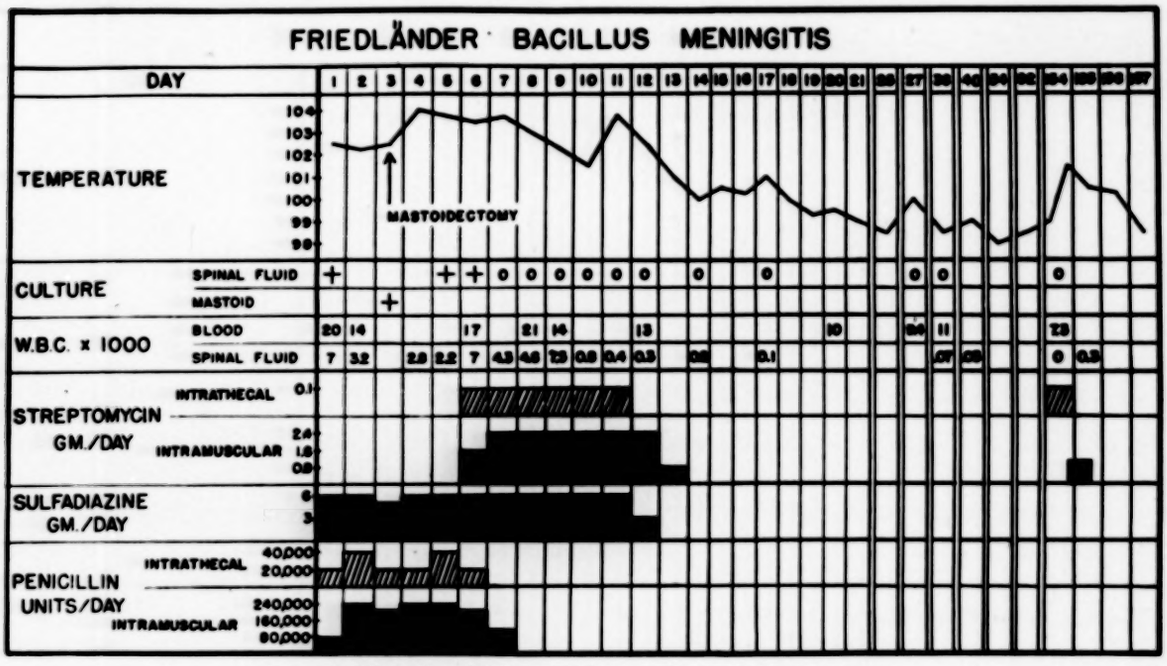

FIG. 1. Clinical and laboratory data relevant to case report.

gested the possibility of sensitivity to sulfadiazine or streptomycin, or both, tests were carried out. The patient was given 2 Gm. sulfadiazine orally and no reaction or temperature rise was observed. Following the spinal tap which yielded the clear, acellular fluid, 0.1 Gm. streptomycin in 10 cc. saline was again injected intrathecally, and the patient complained of poorly localized back pain for a few moments. Within the next hour, the temperature rose to 101°F., at which time she was started on a series of three intramuscular injections of streptomycin, 0.3 Gm. each, over a twelve-hour period. The temperature remained elevated at 101°F. for thirty-six hours and returned to normal only after streptomycin had been discontinued for twenty-eight hours. Before discharge the lumbar puncture was repeated and at this time the fluid was found to contain 260 white cells/mm.^{3}, 75 per cent of which were lymphocytes. Whether or not the febrile and cytologic response represented a sensitivity reaction to or the local irritating effect of streptomycin on the meninges was not clearly established.

Comment. It appears clear that in this case, cure resulted from the use of streptomycin. Before the etiologic diagnosis of Friedländer bacillus infection was established the patient remained critically ill for six days in spite of administration of penicillin and sulfadiazine and the performance of mastoidectomy. Sterilization of the spinal fluid was achieved after the first intrathecal dose of streptomycin, and from that time rapid improvement was obvious both in the clinical picture and in the diminishing glycosuria under lower insulin dosage. The fact that the patient, in retrospect, appears to have exhibited a sensitivity to or an irritative reaction to streptomycin both with febrile response and with spinal fluid pleocytosis does not seem to have reduced the therapeutic effect of the drug in any way.

The prolonged finding of cells in the cerebrospinal fluid for six weeks following streptomycin therapy with 33 lymphocytes/mm.^{3} still present at the time of discharge may have been due to the drug or to the slow resolution of the extensive infection. It is interesting to note that when the intrathecal test dose on a return visit resulted in a sterile reaction in the cerebrospinal fluid, the pleocytosis was largely lymphocytic rather than granulocytic. This finding has also been noted and commented upon by Logan and Herrell[5] who recently reported a case of influenzal meningitis in which streptomycin therapy was followed by a persistence of lymphocytes in the spinal fluid until the time of discharge.

The value of the use of streptomycin in experimental Friedländer bacillus infections has been shown by Heilman[6] and its use in clinical cases is now being reported. It cannot be doubted that sulfadiazine is also a valuable drug against this organism but whether or not its combination with the antibiotic is desirable remains to be determined. In this case it appeared to be ineffectual when used alone but it was continued during streptomycin therapy. Alkalinization of the urine with the use of sodium bicarbonate appears wise[7] since both of these drugs show decreased renal toxicity with a urinary pH over 7 and streptomycin appears to be more active in an alkaline medium.[8] It seems probable that the combination of streptomycin and sulfadiazine is the treatment of choice for Friedländer bacillus infections at the present time.

FRIEDLÄNDER BACILLUS INFECTIONS IN THE DIABETIC GROUP

In reviewing the literature on Friedländer bacillus meningitis we have been impressed by the association between this infection and diabetes mellitus. In the series tabulated by Ransmeier and Major,[1] five of the thirty cases occurred in individuals who were known to have diabetes or appeared to have had previously unsuspected diabetes prior to the occurrence of the Friedländer bacillus infection. In many of the remaining twenty-five cases the clinical information supplied is insufficient to allow decision as to whether or not diabetes existed so that this group may actually be larger than estimated. Of the three additional cases reported since that time,[2–4] that of Macky and Morris[3] again appears to

represent the infection in association with diabetes. Although the details supplied in this report are few and no urinary findings are included, it is mentioned that the blood sugar level a few days prior to exitus was 268 mg. per cent and that following intravenous use of 500 cc. of 20 per cent glucose and 100 units insulin, the blood sugar readings fell to 115 and 144 mg. per cent. The probability that diabetes existed in this case is suggested by the hyperglycemic figures just listed.

TABLE I

CONDENSED SUMMARY OF THE LITERATURE ON ALL TYPES OF FRIEDLÄNDER BACILLUS INFECTIONS IN RELATION TO THE MENTION OF THE PRESENCE OR ABSENCE OF DIABETES

	Total	Diabetic	Non-diabetic	Not Stated
All cases	293	24	106	163
Pediatric cases (under 10 yr.)	25	?	?	25
Pulmonary cases	223	8	60	155
Extrapulmonary cases	45	16	21	8

Because of the simultaneous occurrence of diabetes and Friedländer bacillus meningitis now reported in 7 or 20 per cent of the thirty-four cases in the literature, we have attempted to determine the incidence of this combination by a detailed examination of the published reports of Friedländer bacillus infections of all types. Unfortunately the clinical protocol of the reported case is too infrequently incomplete with respect to the presence or absence of glycosuria or hyperglycemia. Most of the papers dealing with cases of pulmonary Friedländer infection report them in summary form, omitting individual laboratory details. In spite of this, however, an inspection of the available material shows an association between diabetes and Friedländer infection which is particularly striking in the disseminated or hematogenous, non-pulmonary types of the infection while in the purely pulmonary forms of this infection, both acute and chronic, alcoholism, cirrhosis of the liver, bronchiectasis, carcinoma, tuberculosis, arteriosclerosis, senility and debilitation appear to provide more favorable soil.

In an attempt to document the frequency of the association of diabetes and Friedländer bacillus infection as found in the literature we have reviewed and tabulated all the reported English-written cases since the first volume of the Index Medicus of 1916, with no selection of material during this thirty-year interval. All cases are included, and the occurrence of diabetes is listed as "not stated" only when clinical information is completely lacking and, although not specifically stated, the more complete protocols are considered to represent non-diabetic individuals.

TABLE II

INCIDENCE OF DIABETES IN ALL COMPLETELY REPORTED CASES OF FRIEDLÄNDER BACILLUS INFECTIONS

	Total	No. Diabetic, Per Cent	Non-diabetic, Per Cent
All stated cases	105	24 (23)	81 (77)
Pulmonary cases	68	8 (12)	60 (88)
Extrapulmonary cases	37	16 (43)	21 (57)

Table I indicates the source material from which the more significant figures of Table II were obtained. It may be noted that in 56 per cent of the case reports the information supplied is too incomplete to allow classification with respect to the presence or absence of diabetes. It can also be seen in Table I that most of the "non-stated" cases fall into the pediatric and pulmonary forms of the disease. In Table II the "non-stated" cases of Table I have been eliminated. In this group, 23 per cent of the 105 cases of all types of Friedländer infection occurred in diabetic individuals. When the data are further analyzed, it may be noted that the incidence of diabetes among the pulmonary and extrapulmonary cases is significantly different: of sixty-eight pulmonary and thirty-seven extrapulmonary cases, 12 per cent and 43 per cent, respectively, were diabetic. These figures, par-

ticularly in the latter group, are significant enough to indicate that the association between the metabolic disorder and the bacterial infection is greater than that expected from chance.

COMMENTS

Diabetes has long been recognized as a disease predisposing to infection, most notoriously by the staphylococcus and streptococcus[9] and the tubercle bacillus,[10] and to this group the Friedländer bacillus should be added. There is no comment in the literature as to what circumstance, or set of circumstances, favors this specificity of infection.

In a search for the possible reason for this association the first and most obvious consideration suggests that the biochemical alterations seen in diabetes in some way enhance the bacteriologic growth or virulence of the selected organism or impair some factor in the defense mechanism of the patient.

The close relationship which exists between bacterial encapsulation and pathogenicity has long been recognized. The so-called soluble-specific-substance of the Friedländer bacillus capsule was studied by Goebel[11] and found to be a nitrogen-free, amorphous compound composed of a complex carbohydrate polymer containing hexose and hexuronic acids in varying proportions. It was shown by Avery, Heidelberger and Goebel[12] that the capsular polysaccharide of the type A Friedländer bacillus resembled that of the type III pneumococcus in some of its chemical properties, and that the type B Friedländer bacillus and the type II pneumococcus shared, in addition, an immunologic similarity.

Without the capsule, the Friedländer bacillus is an avirulent, gram-negative organism which is difficult to identify and can easily be confused with bacteria of the coli-aerogenes group. Osterman and Rettger[13] point out that in the avirulent, acapsular phase the Friedländer, aerogenes and coli bacilli are indistinguishable, and if isolated in this form the Friedländer bacillus would probably remain unrecognized. It has been observed by Julianelle[14] and others that the R (rough) or acapsular variants are rarely encountered in human infections, and then most frequently in the chronic, low grade and less virulent disease syndromes, most of which are seen in the pulmonary form.

Julianelle[14] was able to convert cultures of virulent mucoid (M), well encapsulated Friedländer bacilli into a rough (R), nonpathogenic colony by serial passage through impoverished media. However, he could not effect the transfer from R to M forms by using rapid transfers through mice, meat infusion broth or dextrose broth and concluded that the process was probably reversible but that he had not supplied the proper stimulus.

In an attempt to determine the conditions under which the Friedländer bacillus formed capsules, Hoogerheide[15] in 1939 studied the influence of sugar in bacterial environment. He demonstrated that carbohydrate in the medium was not strictly necessary for capsule formation, but that capsules formed without carbohydrate were small and difficult to detect. With added sugar, however, large capsules appeared and colonies became mucoid, and he demonstrated that the glucose of the culture medium actually became a component of the capsular substance. It is significant that Hoogerheide found that at least 0.3 per cent glucose was necessary in the medium for well encapsulated bacteria to be formed, but that other sugars did not favor capsule formation as well. With smaller amounts of glucose available, encapsulation continued until all sugar had been utilized, but from that point bacterial growth and capsular formation were independent functions and could be separately stimulated by different factors.

The pH for growth of Friedländer bacilli was found to range between 5 and 9 with the optimal level at 7.5, but encapsulation appeared to be independent of pH. The optimal temperature for capsule formation was found to be 37°C., with the range extending to 42°C.

The conditions just described may be of some significance in promoting the occurrence of virulent, pathogenic Friedländer bacilli in the tissues of diabetic individuals. The minimal carbohydrate requirement in culture media of 300 mg. per cent for capsule formation is above the concentration of glucose in the body fluids and tissues of the normal individual, but may often be afforded by patients with diabetes. The optimal pH and temperature found by Hoogerheide are also at the physiologic levels, and the ranges are not exceeded by changes seen either in health or disease.

Although the cultural conditions just cited for development, *in vitro*, of encapsulation and virulence of Friedländer bacilli may play only a partial rôle if any in promoting the relatively high incidence of this infection in patients with diabetes, the occurrence of excessive sugar in each instance serves as a source of interesting speculation with regard to the apparent specificity of the bacterium-patient relationship discussed in this article.

SUMMARY

1. A case of Friedländer bacillus meningitis successfully treated with streptomycin is presented. Although sulfadiazine was used in conjunction with streptomycin, it was totally ineffective when used alone prior to the addition of streptomycin therapy.

2. In thirty-four cases of Friedländer bacillus meningitis collected from the literature, the following recoveries are recorded: (1) One before chemotherapy, a thirty-four year old male reported by Rothschild[16] in 1931. Otitis media complicated by mastoiditis and subdural abscess was thought to be the primary focus, and recovery followed surgical drainage. The patient had diabetes. (2) A two year old Cuban child reported by Montes and Real[17] in 1940. Cure followed administration of sulfapyridine. (3) A forty-nine year old male reported by Robertson[18] in 1941. Maxillary sinusitis was thought to be the primary focus for the meningitic infection in this case, and cure again resulted after the use of sulfapyridine. This patient also had diabetes. (4) A twenty-six month old infant reported by Mori[2] in 1943, with recovery following use of a sulfonamide (soluseptazine). (5) The case reported by Tartakoff, Grynbaum and LeCompte[4] in 1946 followed craniotomy for brain tumor and was treated with streptomycin. Although the patient died suddenly of pulmonary embolization, the postmortem findings suggested that the antibiotic had probably been successful in controlling the infection. (6) The case reported in this article represents the sixth recovery among these thirty-four cases.

3. Of the thirty-four cases just mentioned the reported information is sufficiently definite to indicate that seven had diabetes.

4. In all types of Friedländer bacillus infections an analysis of the completely reported cases (Table II) indicates the occurrence of diabetes in 23 per cent of all types of Friedländer bacillus infections, in 12 per cent of pulmonary cases and in 43 per cent of extrapulmonary cases such as meningitis, liver abscess and septicemia.

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Book Reviews

The Pathology of Nutritional Disease. By Richard H. Follis, Jr., M.D. Pp. 291. Springfield, Ill., 1948. Charles C. Thomas. *Price* $6.75.

This book is the first monographic presentation covering the pathologist's findings and the pathologist's point of view on the changes which occur as a result of nutritional deficiencies. As such, it is an invaluable aid to the experimental investigator in all fields which touch on nutrition. The author, now Associate Professor of Pathology at the Johns Hopkins Medical School, has had a rare background involving both experimental and observational experience in animal experimentation and the professional training of the pathologist. Dr. Follis' own publications in the field convey to the nutrition biochemist the assurance of the author's grasp of the technical phases of this special field and his interest in its aims.

To the medical man the book should be particularly welcome since it gives, in a connected account, a competent, very condensed statement of essential biochemical information and the pathologic consequences of deficiencies. Each topic ends with a statement of what is known concerning the rôle of the particular factor in human nutrition.

On the subject of deficiency states in man Dr. Follis' attitude is a critical one in the sense that he gives no space to the large mass of material published in clinical journals based on tentative evidence, casual thinking and hopeful attitudes. Dr. Follis is distinctly of the generation which includes the physiologic with the morphological changes in a consideration of pathology and it is therefore somewhat unexpected to read: "However, as one who continually observes disease at the autopsy table it is not possible —except in the case of scurvy and rickets in infants—to be other than conservative, a leaning which perhaps has some virtue in the days of vitamin inflation." One might well ask: "Is the autopsy table the court of appeal?" even if one grants its advantages and its motives without any hesitation.

The plan of the book is simple and common sense prevails in the selection and arrangement of material. The author has struck a satisfying medium between the two functions of a book of this kind, namely, the cataloguing of material and the presentation of a line of thought, with the result that the book is decidedly readable. For some time to come this work will also be the most ready reference volume for topics in nutritional pathology. For this it is fitted with its selected bibliography of 791 references and two competent indexes.

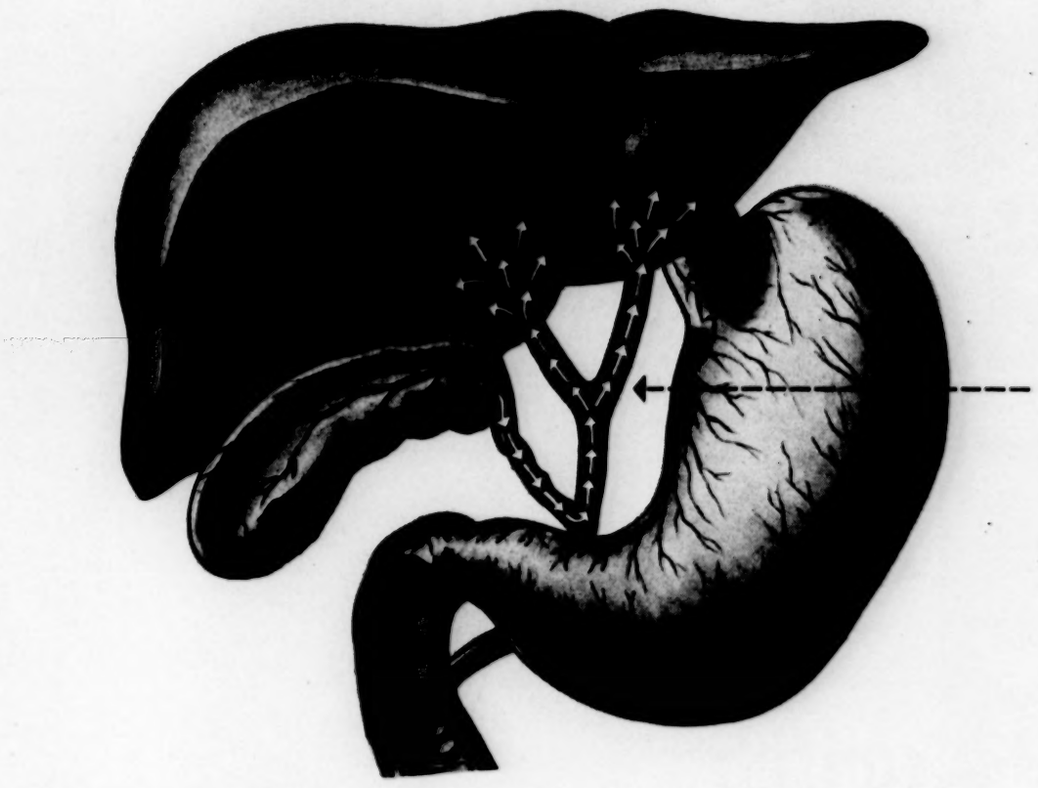
T.F.Z.

Unipolar Lead Electrocardiography. By Emanuel Goldberger, M.D. Pp. 182. Philadelphia, 1947. Lea and Febiger. *Price* $4.00.

Dr. Goldberger has written a concise, scholarly monograph on the subject of electrocardiography particularly as concerns the unipolar lead. In so doing he has contributed a great deal toward the ultimate clarification of the physiologic mechanisms involved in the science of electrocardiography. This aspect has been well handled and should prove helpful to those whose use of the electrocardiograph is more than casual. The value of the work would appear to be greatest in this respect since the author does not present a preponderance of evidence that would justify the routine use of the unipolar lead itself.

The book has been carefully assembled, the cuts are excellent and the bibliography is complete.

J.M.B



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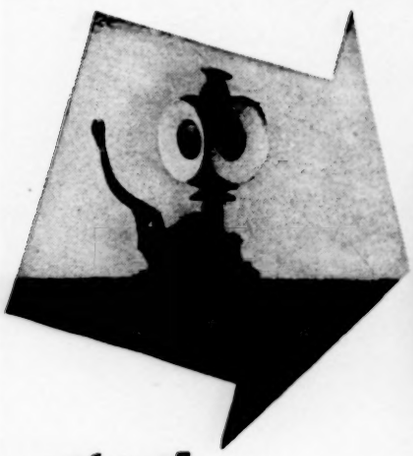

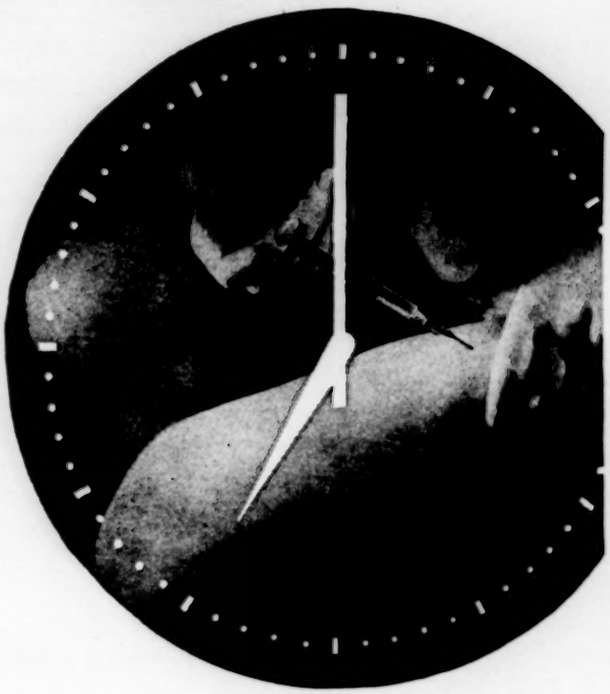

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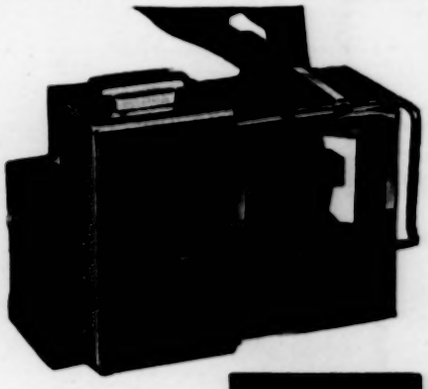

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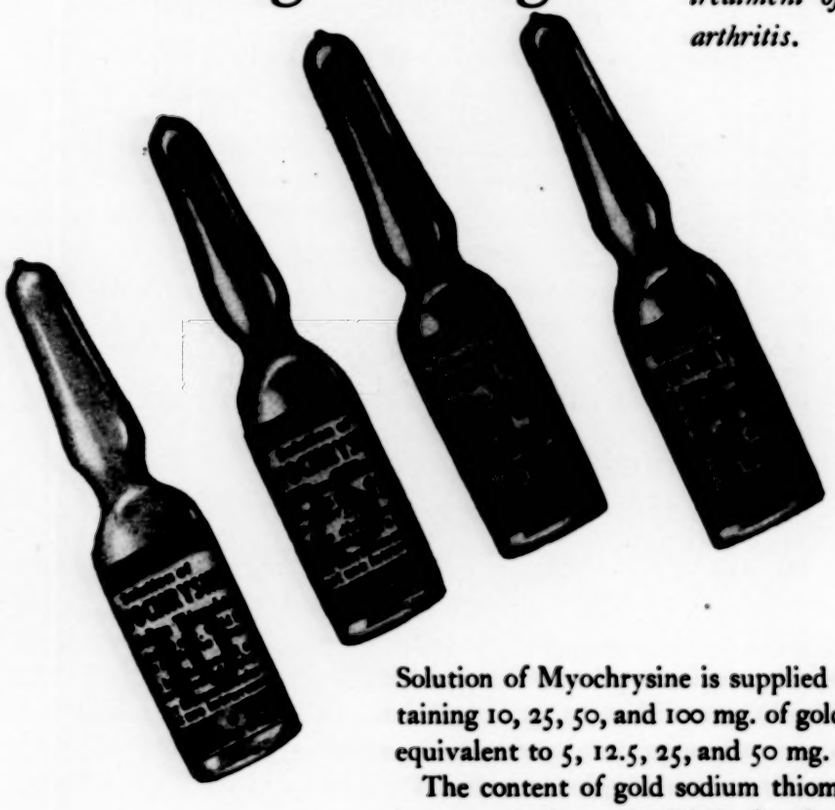

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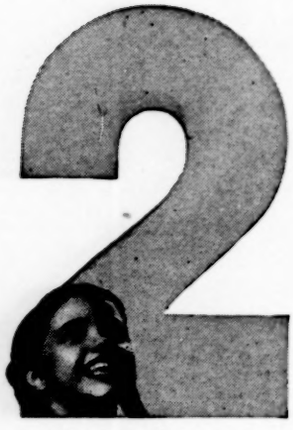
Here are 3 reasons why

Eskadiazine is so widely prescribed



It is so palatable that all types of patients actually like to take it. Children say: "It tastes good."

It is absorbed so rapidly that desired serum levels are attained in 2 hours, instead of the 6 required for sulfadiazine in tablet form.

Your patients will be grateful to you for prescribing this easy-to-take sulfadiazine.

Eskadiazine

the outstandingly palatable fluid sulfadiazine

Smith, Kline & French Laboratories, Philadelphia

relief

from the nausea and vomiting of pregnancy

A well supported approach

Effective control of the distressing nausea and vomiting of pregnancy is readily obtained with Sempylex. Based on the therapeutic efficacy of pyridoxine which has been repeatedly shown to bring gratifying relief in emesis gravidarum, Sempylex offers more than pyridoxine therapy. The presence of significant amounts of glucose, together with thiamine, riboflavin and niacinamide, aids the action of pyridoxine by promoting carbohydrate metabolism and glycogen storage. Systemic acidosis is thus counteracted and liver function, which appears involved in this condition, is improved.

Sempylex, employing a truly physiologic approach, precludes undesirable side actions on mother and child. Recommended dosage, 1 tablespoonful 4 times daily.

THE S. E. MASSENGILL COMPANY
Bristol, Tenn.-Va.
NEW YORK • SAN FRANCISCO • KANSAS CITY

SE Co

Sempylex

for liver damage **MEONINE®**

(dl-methionine Wyeth)

IMPORTANT WYETH ADDITION TO *New and Nonofficial Remedies*

Realizing that traditional management of severe liver disease has been on the whole disheartening, Wyeth has for years been conducting research on the essential amino acid most concerned with liver function . . . dl-methionine.

Product of this research is Meonine.

Meonine may be used to supplement the protein-rich diet usually prescribed whenever the liver has been damaged by malnutrition, alcoholism, pregnancy, allergy, or toxins. And it is clearly indicated if this diet cannot be taken. There is no evidence, however, that Meonine is more effective than foodstuffs such as casein and egg white which contain pure methionine.

In early stages of cirrhosis, clinical results with Meonine have been most encouraging. Complete directions for use and bibliography supplied on request.

Wyeth ®

Meonine supplied in 0.5 gram tablets, bottles of 100 and 1000. Crystalline Meonine—for preparing injection solutions—supplied in 50 gram bottles.

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